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Official

December 18, 2007

Our Docket No.: 868_012

To: Magdalen Greenlief Fax No.: (571) 273-0125
From: Stephen P. Burr Fax No.: (315) 233-8320
Re: In re the Application of: Noriaki KATO, Hiroshi NAGANO, Kaori TANIKO and Takahito JOMORI
Serial No.: 10/587,320 Art Unit: 4173
Date Filed: May 10, 2007 Conf. No. 4731
Title: PROPHYLACTIC OR THERAPEUTIC AGENT FOR DIABETIC MACULOPATHY

I hereby certify that the following page(s) including this cover is/are being transmitted via facsimile to Magdalen Greenlief at (571) 273-0125 at the Patent and Trademark Office on *December 18, 2007*:

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	Total Pages		69

Elizabeth A. VanAntwerp

*These headings correspond to the headings on Form PTO/SB/20.

PTO/SB/20 (09-07)

Approved for use through 12/31/2008. OMB 0651-0058
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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**REQUEST FOR PARTICIPATION IN THE PATENT PROSECUTION HIGHWAY (PPH) PILOT PROGRAM
BETWEEN THE (1) JPO OR (2) UKIPO, AND THE USPTO**

Application No.:	10/587,320	First Named Inventor:	Noriaki KATO
Filing Date:	May 10, 2007	Attorney Docket No.:	868_012
Title of the Invention:	PROPHYLACTIC OR THERAPEUTIC AGENT FOR DIABETIC MACULOPATHY		

**THIS REQUEST FOR PARTICIPATION IN THE PPH PILOT PROGRAM MUST BE FAXED TO:
THE OFFICE OF THE COMMISSIONER FOR PATENTS AT 571-273-0125 DIRECTED TO THE ATTENTION OF MAGDALEN GREENLIEF**

APPLICANT HEREBY REQUESTS PARTICIPATION IN THE PATENT PROSECUTION HIGHWAY (PPH) PILOT PROGRAM AND PETITIONS TO MAKE THE ABOVE-IDENTIFIED APPLICATION SPECIAL UNDER THE PPH PILOT PROGRAM.

The above-identified application validly claims priority under 35 U.S.C. 119(a) and 37 CFR 1.55 to one or more corresponding JPO application(s) or UKIPO application(s).

The ☒ JPO ☐ UKIPO application number(s) is/are: PCT/JP2005/001187 (Japanese Application No. 2005-517502)

The filing date of the ☒ JPO ☐ UKIPO application(s) is/are: PCT filing date is January 28, 2005 (National Stage entry date is July 13, 2006)

I. List of Required Documents:

- a. A copy of all JPO office actions (excluding "Decision to Grant a Patent") in the above-identified JPO application(s), or a copy of all UKIPO office actions in the above-identified UKIPO application(s).

☒ Is attached.

☐ Is available via Dossier Access System. Applicant hereby requests that the USPTO obtain these documents via the Dossier Access System.

*It is not necessary to submit a copy of the "Decision to Grant a Patent" and an English translation thereof.

- b. A copy of all claims which were determined to be patentable by the JPO in the above-identified JPO application(s), or a copy of all claims which were determined to be patentable by the UKIPO in the above-identified UKIPO application(s).

☒ Is attached.

☐ Is available via Dossier Access System. Applicant hereby requests that the USPTO obtain these documents via the Dossier Access System.

- c. English translations (where applicable) of the documents in a. and b. above along with a statement that the English translations are accurate are attached.

Information disclosure statement listing the documents cited in the JPO office actions or UKIPO office actions is attached.

Copies of all documents are attached except for U.S. patents or U.S. patent application publications.

[Page 1 of 2]

The collection of information is required by 35 U.S.C. 119, 37 CFR 1.55, and 37 CFR 1.102(d). The information is required to obtain or retain a benefit by the public, which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. FAX COMPLETED FORMS TO: Office of the Commissioner for Patents at 571-273-0125, Attention: Magdalen Greenlief.

PTO/SB/20 (09-07)

Approved for use through 12/31/2008. OMB 0851-0058

U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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**REQUEST FOR PARTICIPATION IN THE PATENT PROSECUTION HIGHWAY (PPH) PILOT PROGRAM
BETWEEN THE (1) JPO OR (2) UKIPO, AND THE USPTO**
(continued)

Application No.:

10/587,320

First Named Inventor:

Noriaki KATO

II. Claims Correspondence Table:

Claims in US Application	Patentable Claims in JP/UKIPO Application	Explanation regarding the correspondence
10*	1	(*as amended on December 18, 2007)
11	-	there is no claim in JP 2005-517502 that corresponds to claim 11 in USSN 10/587,320
12	2	
13	3	
14	4	

III. All the claims in the U.S. Application sufficiently correspond to the patentable/allowable claims in the JPO or UKIPO application.

IV. Payment of Fees:

The Commissioner is hereby authorized to charge the petition fee under 37 CFR 1.17(h) (\$130.00) as required by 37 CFR 1.102(d) to: ☒ Deposit Account No.: 50-1446.

☐ Credit Card. Credit Card Payment Form (PTO-2038) is attached.

Signature

Date

December 18, 2007

Name
(Print/Typed)

Stephen P. Burr

Registration Number

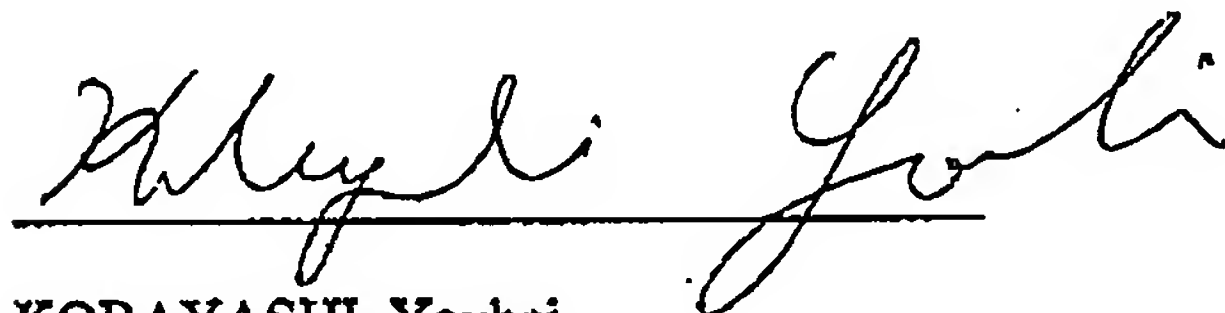
32,970

U.S. Patent Application Serial No. 10/587,320

TRANSLATOR'S CERTIFICATE

I, KOBAYASHI Youhei, certify that I am qualified to translate documents from the Japanese Language into the English Language, and I verify that the attached English translation of Amendment on 14th May 2007 is accurate.

Date Nov. 129 / 2007

A handwritten signature in cursive script, appearing to read 'Youhei Kobayashi', is written over a horizontal line.

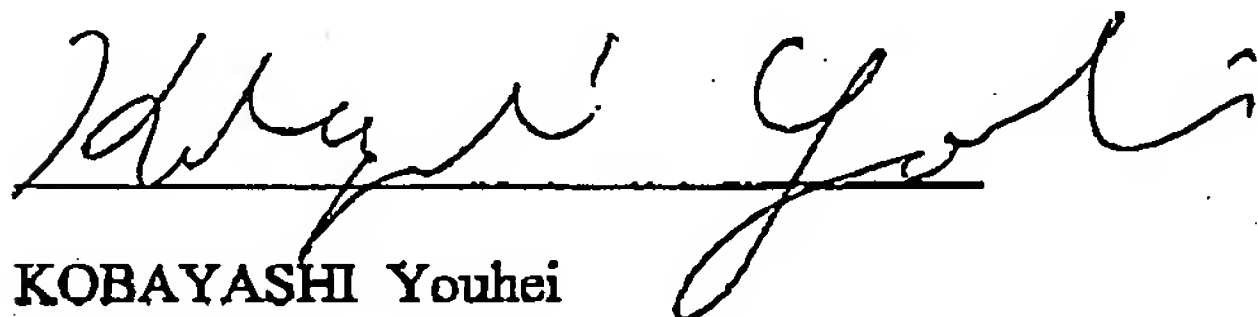
KOBAYASHI Youhei

U.S. Patent Application Serial No. 10/587,320

TRANSLATOR'S CERTIFICATE

I, KOBAYASHI Youhei, certify that I am qualified to translate documents from the Japanese Language into the English Language, and I verify that the attached English translation of EXPLANATION OF CIRCUMSTANCES CONCERNING ACCELERATED EXAMINATION on 15th May 2007 is accurate.

Date Nov. 129 12007

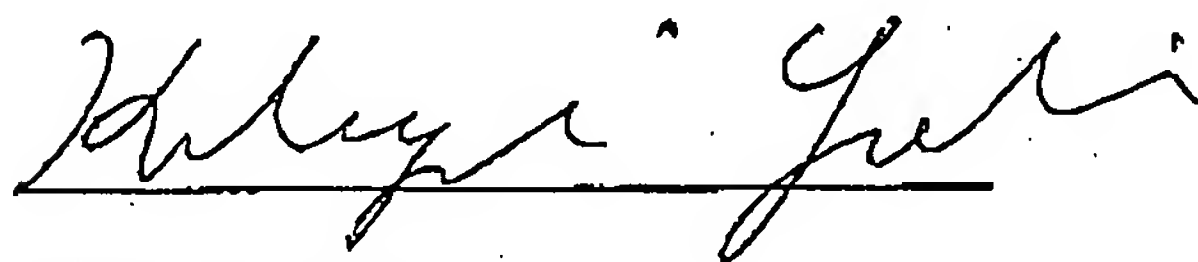

KOBAYASHI Youhei

U.S. Patent Application Serial No. 10/587,320

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I, KOBAYASHI Youhei, certify that I am qualified to translate documents from the Japanese Language into the English Language, and I verify that the attached English translation of NOTIFICATION OF REASONS FOR REFUSAL on 18th July 2007 is accurate.

Date *Nov. 129 / 2007*

A handwritten signature in cursive script, appearing to read 'Youhei Kobayashi', is written over a horizontal line.

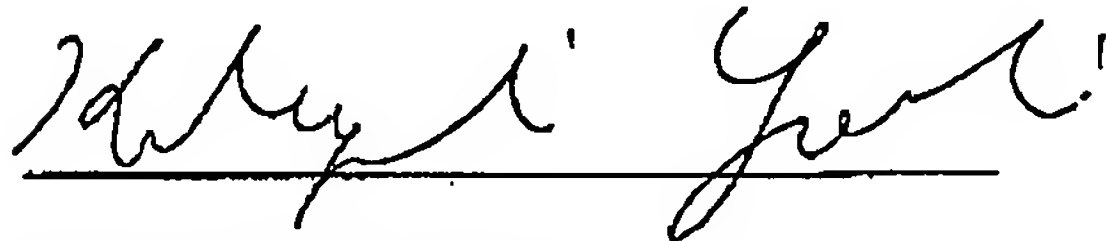
KOBAYASHI Youhei

U.S. Patent Application Serial No. 10/587,320

TRANSLATOR'S CERTIFICATE

I, KOBAYASHI Youhei, certify that I am qualified to translate documents from the Japanese Language into the English Language, and I verify that the attached English translation of Amendment on 3rd August 2007 is accurate.

Date Nov. 129 / 2007

A handwritten signature in cursive script, appearing to read 'Kobayashi Youhei', is written over a horizontal line.

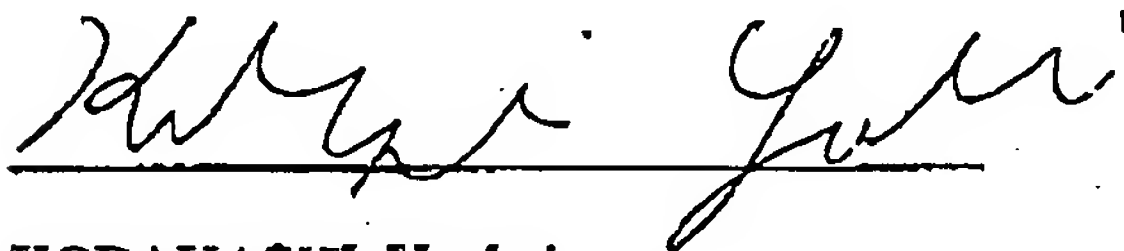
KOBAYASHI Youhei

U.S. Patent Application Serial No. 10/587,320

TRANSLATOR'S CERTIFICATE

I, KOBAYASHI Youhei, certify that I am qualified to translate documents from the Japanese Language into the English Language, and I verify that the attached English translation of NOTIFICATION OF ALLOWANCE on 27th August 2007 is accurate.

Date *Nov. 129, 2007*

A handwritten signature in cursive script, appearing to read 'Youhei Kobayashi', is written over a horizontal line.

KOBAYASHI Youhei

[Document Name] AMENDMENT
[Reference] P06023SKK
[Filing Date] 14th May 2007
[Address] To the Commissioner, Patent Office

5 [Case Identification]

[Application Number] Patent Application No. 2005-517502
[Amender]

[Identification Number] 000144577

[Name] SANWA KAGAKU KENKYUSHO CO., LTD.

10 [Agent]

[Identification Number] 100108280

[Patent Attorney]

[Name] KOBAYASHI Youhei

[Telephone] 0594-27-5515

15 [Amendment 1]

[Amended Document] CLAIMS

[Amended Item] Whole Document

[Amending Method] Modification

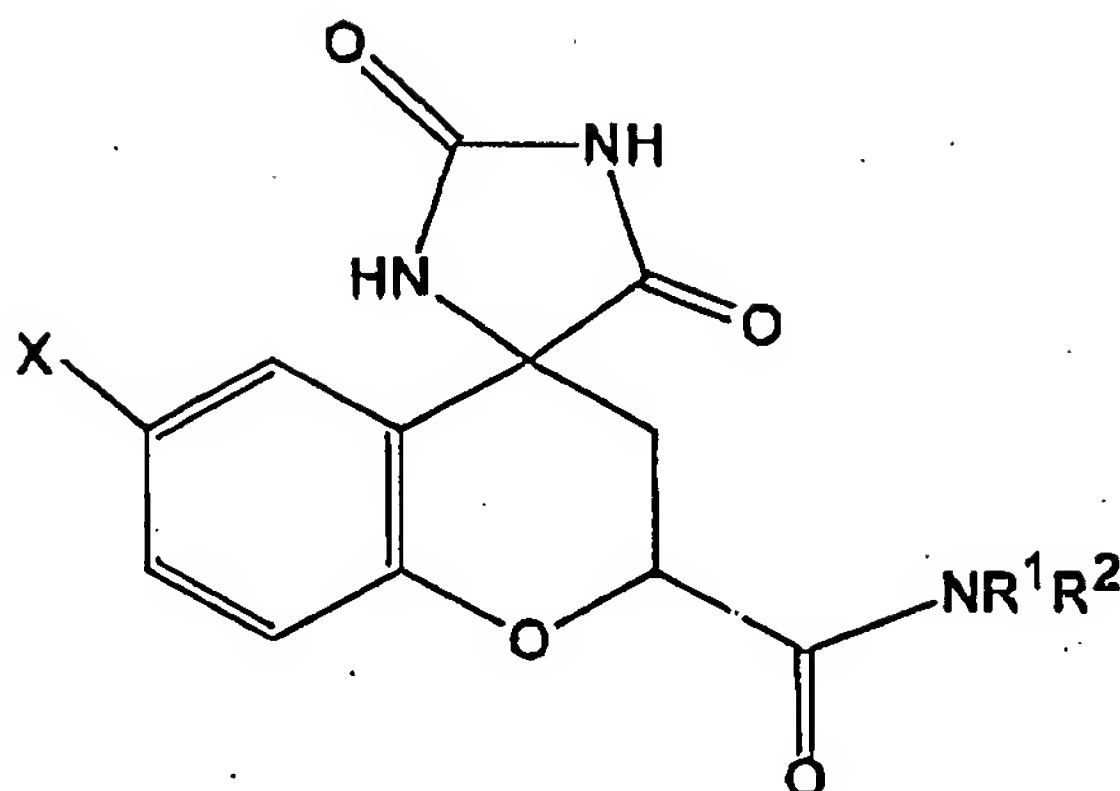
[Amendment Contents]

20 [Document Name] CLAIMS

[Claim 1]

A prophylactic or therapeutic agent for diabetic maculopathy, comprising, as an active ingredient, a compound represented by the general formula:

25 [Chemical Formula 1]



(wherein X represents a halogen or a hydrogen atom, R¹ and R² concurrently or differently represent a hydrogen atom or an optionally substituted C1 to C6 alkyl group, or R¹ and R² together with a nitrogen atom bound thereto and optionally another nitrogen atom or an oxygen atom, are combined to form a 5- to 6-membered heterocycle).

[Claim 2] The prophylactic or therapeutic agent for diabetic maculopathy according to claim 1, wherein the compound is (2S, 4S)-6-fluoro-2', 5'-dioxospiro [chroman-4, 4'-imidazolidine]-2-carboxamide.

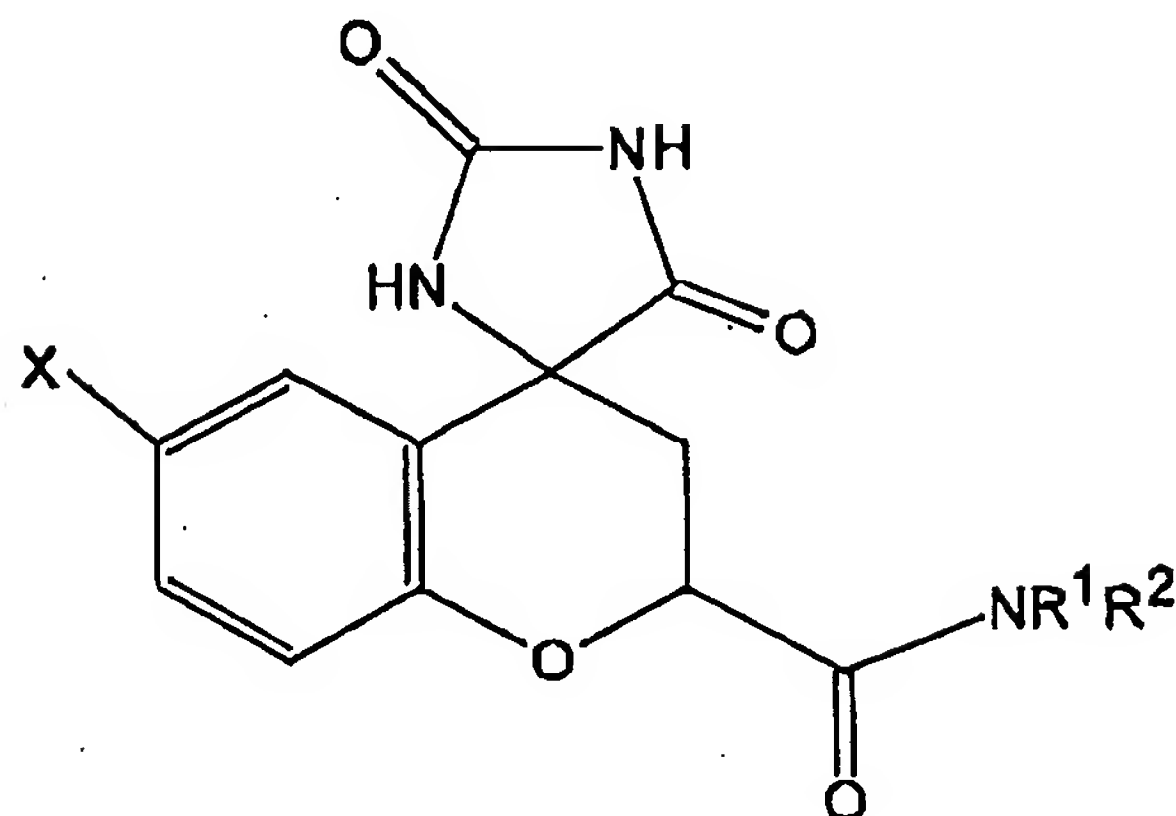
[Claim 3] The prophylactic or therapeutic agent for diabetic maculopathy according to claim 1 or 2, which is for use in macular edema or in retinal pigment epitheliopathy in diabetic maculopathy.

[Claim 4] The prophylactic or therapeutic agent for diabetic maculopathy according to claim 1 or 2, which is for use as an agent for improving visual acuity or inhibiting deterioration of visual acuity in diabetic maculopathy.

[Claim 5] An agent for improving visual acuity or inhibiting deterioration of visual acuity in diabetic maculopathy,

comprising, as an active ingredient, a compound represented by the general formula:

[Chemical Formula]



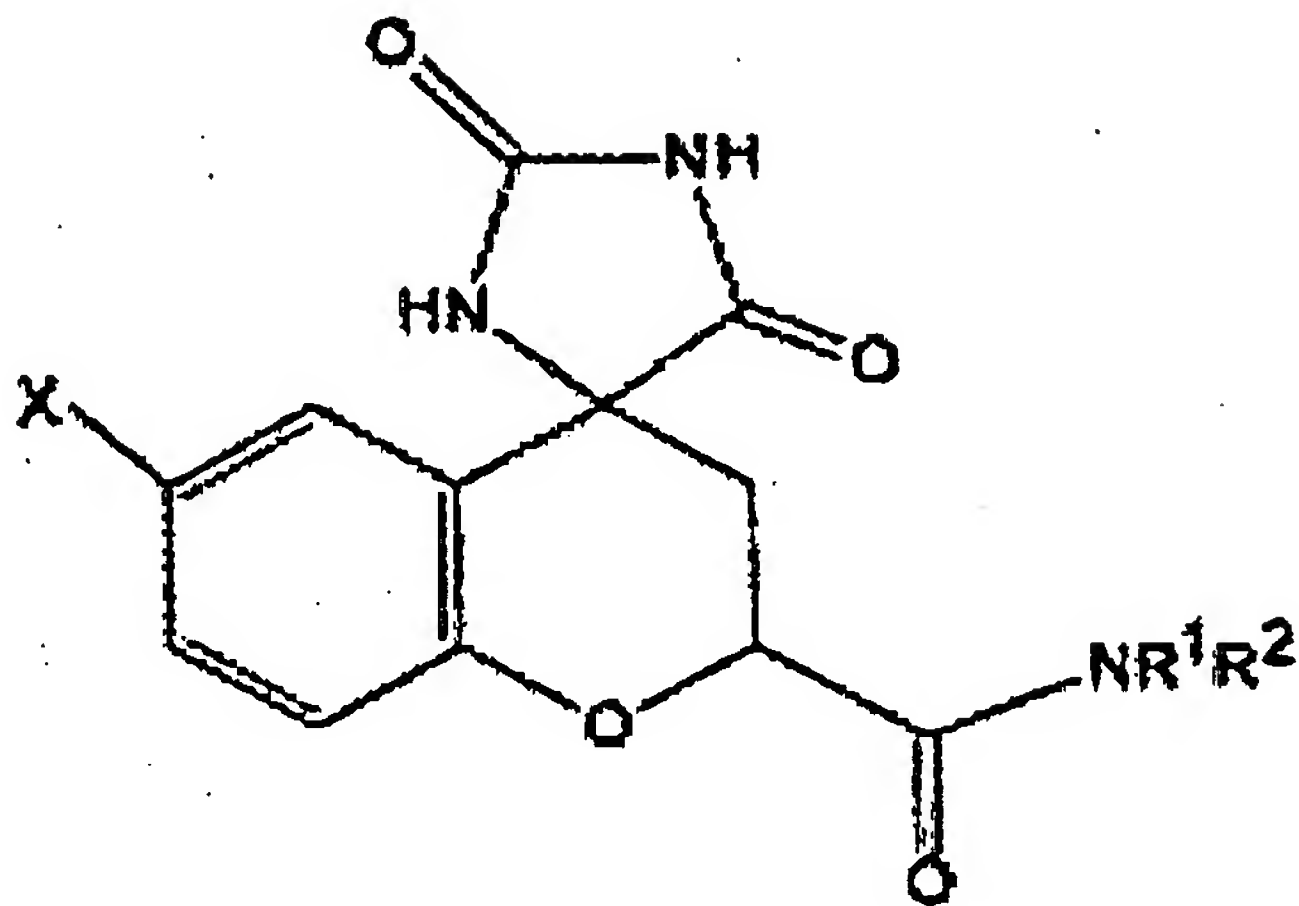
- 5 (wherein X represents a halogen or a hydrogen atom, R¹ and R² concurrently or differently represent a hydrogen atom or an optionally substituted C1 to C6 alkyl group, or R¹ and R² together with a nitrogen atom bound thereto and optionally another nitrogen atom or an oxygen atom, are combined to form a 5- to
10 6-membered heterocycle).

[Claim 6] The agent for improving visual acuity or inhibiting deterioration of visual acuity in diabetic maculopathy, according to claim 5, wherein the compound is (2S, 4S)-6-fluoro-2', 5'-dioxospiro

- 15 [chroman-4, 4'-imidazolidine]-2-carboxamide.

【書類名】 手続補正書
【整理番号】 P 0 6 0 2 3 S K K
【提出日】 平成 1 9 年 5 月 1 4 日
【あて先】 特許庁長官 殿
【事件の表示】
 【出願番号】 特願 2 0 0 5 - 5 1 7 5 0 2
【補正をする者】
 【識別番号】 0 0 0 1 4 4 5 7 7
 【氏名又は名称】 株式会社 三和化学研究所
【代理人】
 【識別番号】 1 0 0 1 0 8 2 8 0
 【弁理士】
 【氏名又は名称】 小林 洋平
 【電話番号】 0 5 9 4 - 2 7 - 5 5 1 5
【手続補正 1】
 【補正対象書類名】 特許請求の範囲
 【補正対象項目名】 全文
 【補正方法】 変更
 【補正の内容】
 【書類名】 特許請求の範囲
 【請求項 1】 一般式
【化 1】

II (b)(ii)



(式中 X はハロゲン又は水素原子を意味し、R¹ および R² は、同時にあるいは別々に、水素原子、置換されていてもよい C1-6 アルキル基を示すか、又は、R¹ と R² は一緒にて窒素原子と共に或いは更に他の窒素原子又は酸素原子と共に 5 ～ 6 員の複素環を示す。)

で示される化合物を有効成分とする、糖尿病黄斑症の予防又は治療剤。

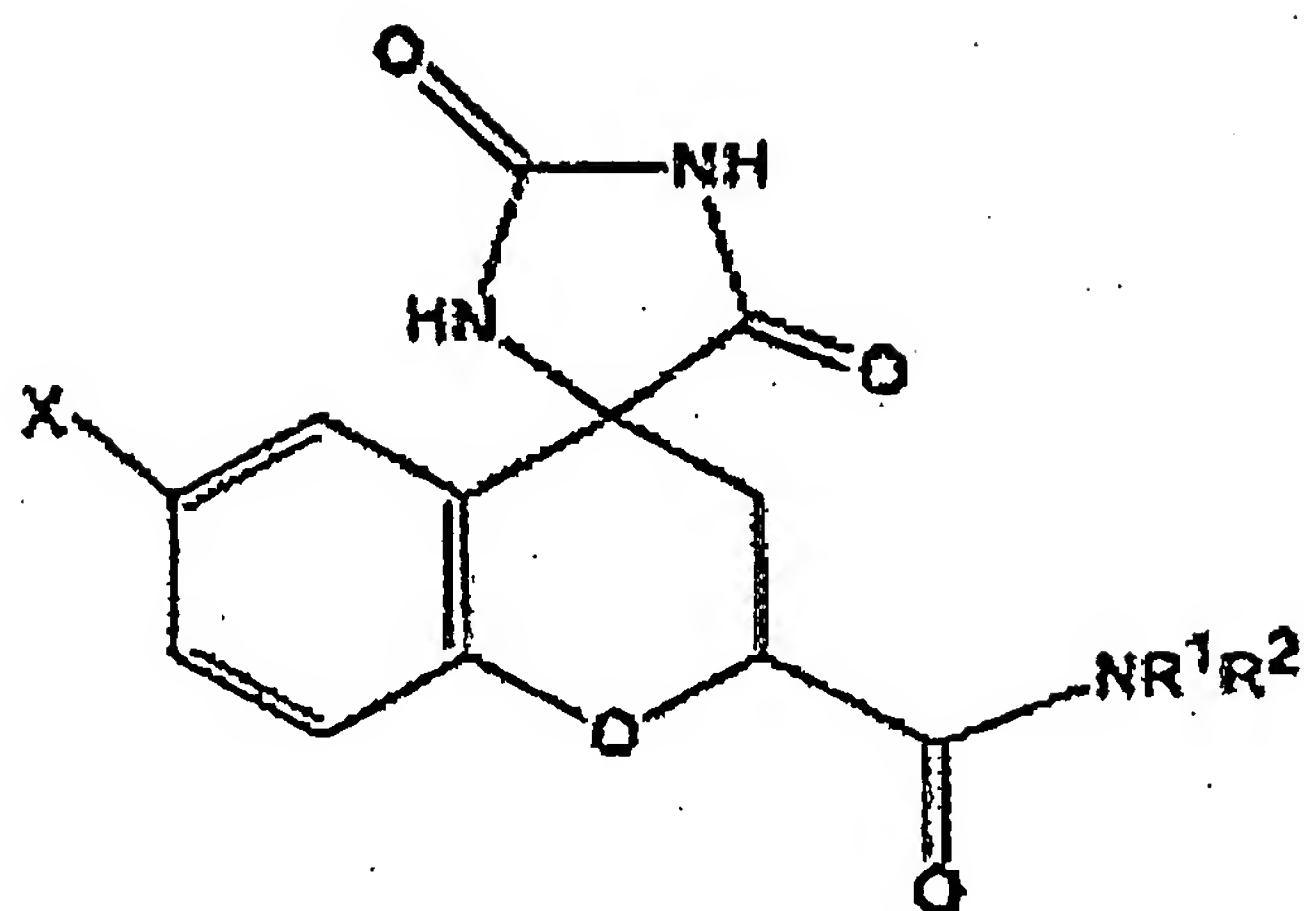
【請求項 2】 化合物が (2S,4S)-6-フルオロ-2',5'-ジオキソスピロ[クロマン-4,4'-イミダゾリジン]-2-カルボキサミドである、請求項 1 に記載の糖尿病黄斑症の予防又は治療剤。

【請求項 3】 糖尿病黄斑症における黄斑浮腫又は糖尿病色素上皮症に使用される、請求項 1 又は 2 に記載の糖尿病黄斑症の予防又は治療剤。

【請求項 4】 糖尿病黄斑症における視力の改善又は低下防止剤として使用される、請求項 1 又は 2 に記載の糖尿病黄斑症の予防又は治療剤。

【請求項 5】 一般式

【化 2】



(式中Xはハロゲン又は水素原子を意味し、R¹およびR²は、同時にあるいは別々に、水素原子、置換されていてもよいC1-6アルキル基を示すか、又は、R¹とR²は一緒にて窒素原子と共に或いは更に他の窒素原子又は酸素原子と共に5～6員の複素環を示す。)

で示される化合物を有効成分とする、糖尿病黄斑症における視力の改善又は低下防止剤。

【請求項6】 化合物が(2S,4S)-6-フルオロ-2',5'-ジオキソスピロ[クロマン-4,4'-イミダゾリジン]-2-カルボキサミドである、請求項5に記載の糖尿病黄斑症における視力の改善又は低下防止剤。

[Document Name] EXPLANATION OF CIRCUMSTANCES CONCERNING
ACCELERATED EXAMINATION

[Filing Date] 15th May 2007

[Reference] P06023SKK

5 [Address] To the Commissioner, Patent Office

[Case Identification]

[Application Number] Patent Application No. 2005-517502

[Filer]

[Identification Number] 000144577

10 [Name] SANWA KAGAKU KENKYUSHO CO., LTD.

[Agent]

[Identification Number] 100108280

[Patent Attorney]

[Name] KOBAYASHI Youhei (Seal)

15 [Telephone] 0594-27-5515

[Statement about Background of Accelerated Examination]

1. Background

Corresponding patent applications have been filed with the
European Patent Office, U.S. Patent and Trademark Office,
20 Chinese Patent Office, Korean Patent Office, Canadian Patent
Office and Australian Patent Office.

The European patent application has been assigned with
application No. 05704239.2. The U.S. patent application has
been assigned with application No. 10/587,320. The Chinese
25 patent application has been assigned with application No.
200580003659.1. The Korean patent application has been assigned
with application No. 10-2006-7015812. The Canadian patent
application has been assigned with application No. 2554679. The

Australian patent application has been assigned with application No. 2005207906.

2. Disclosure and Comparative Explanation of Prior Art

5 (1) Document Names

According to an International Preliminary Examination conducted in the original International Patent Application (PCT/JP2005/1187), the following are documents relevant to the present invention:

10 Document 1: MA Speicher et al., Pharmacologic therapy for diabetic retinopathy, Expert Opinion on Emerging Drugs 2003; 8; 239-250.

Document 2: M Akita et al., Effects of an aldose reductase inhibitor, SNK-860, on the histopathological changes of retinal
15 tissues in a streptozotocin-induced diabetic rat model, Acta Med Okayama 1993; 47: 299-304.

Document 3: JP-A-H07-242547

(2) Comparative Explanation

The present invention has been amended by an Amendment
20 filed on 14th May.

(1) The Invention of Claim 1 and Prior Art Documents

Claim 1 is the invention relating to a prophylactic or therapeutic agent for diabetic maculopathy, which contains, as an effective ingredient, a compound represented by the general
25 formula [Chemical Formula 1]. The compound represented by the general formula contains (2S, 4S)-6-fluoro-2', 5'-dioxospiro [chroman-4, 4'-imidazolidine]-2-carboxamide known as SNK-860 and a group of compounds having a structure similar thereto.

Next, we will explain the prior art documents.

Document 1

describes in the abstract that there is a possibility that proliferative diabetic retinopathy (PDR) and macular edema (ME) can be prevented by glycemic control or amelioration of various abnormalities in the metabolism of sugar (AR inhibitor, antiglycation agent, PKC inhibitor). In fact, it is described that in regard to a PKC inhibitor, development has proceeded for diabetic retinopathy and macular edema and the effectiveness has been confirmed. However, in regard to an aldose reductase inhibitor (AR inhibitor), nothing is described about the effectiveness in macular edema. Moreover, it is described that although animal experiments show the effectiveness of an AR inhibitor in treating diabetic retinopathy, clinical investigation can find no effectiveness of an AR inhibitor (particularly, sorbinil). Thus, the reference shows a negative opinion about the AR inhibitor (page 242, 5 to 9 lines of the left column).

In addition, in documents 2 and 3, it is described that SNK-860 is effective for amelioration of retinal edema or diabetic simple retinopathy based on the results obtained from experimental animal model.

The following will describe what suggestion is given to a person with ordinary skill in the art when the person has read these documents. The person who has read document 1 is considered to recognize that a RKC inhibitor is effective for amelioration of diabetic retinopathy and macular edema but that it is difficult to show by clinical investigation that an AR

inhibitor is effective for amelioration of diabetic retinopathy and macular edema. A document should be determined regarding the described contents after having been read through but should not be determined on the basis of only partial description, i.e. the abstract. The person with ordinary skill in the art knows that clinical investigation in diabetic retinopathy has not shown effectiveness of many AR inhibitors even though the AR inhibitors are effective in animal experiment of diabetic retinopathy. Accordingly, the person is definitely supposed to reach the aforesaid conclusion.

Furthermore, when documents 1, 2 and 3 are combined, the person with ordinary skill in the art must receive the suggestion that in regard to SNK-860, it is difficult to show the effectiveness in clinical investigation of diabetic retinopathy or diabetic maculopathy although it is effective in an experimental animal model of diabetic retinopathy. In other words, the person with ordinary skill in the art will receive the similar suggestion regarding a group of compounds having similar structure, including SNK-860.

As obvious from the foregoing, it is considered that the prior art documents contain no description that motivates the invention of claim 1.

Here, Applicant shows an unpredictable advantageous effect of the invention of claim 1 by experimental data.

A certificate of experimental results which will be described later is a comparison between SNK-860 which is a most typical compound represented by the general formula [chemical formula 1] and epalrestat which is the only drug confirmed to

be effective in treating diabetic retinopathy by the clinical investigation, by using an experimental model of monkeys with diabetic maculopathy. As obvious from the data, epalrestat does not exert an effect when a dose thereof is increased within a
5 range in which drug toxicity does not occur. However, SNK-860 suppresses macular edema even in lower doses. This is a distinguished difference and is said to be an unexpected advantageous effect.

Explaining the diabetic maculopathy again, tissues of the
10 macula and the retina differ in morphology, and diabetic retinopathy and diabetic maculopathy are perceived as quite different diseases in textbooks and cannot be regarded as the same (following document 4). Furthermore, the effectiveness of SNK-860 in diabetic maculopathy has been confirmed by the
15 clinical investigation described in the specification. Accordingly, SNK-860 is not necessarily effective in an experimental model.

Document 4: Hidetoshi Yamashita and Ryo Kawasaki ed., Diabetic Retinopathy: Best Advice By Medical Specialist, Tokyo,
20 Shindann-to-Chryousha, 2003, pages 47-59.

(ii) The Invention of Claim 2 and Prior Art Documents

Claim 2 limits the compound to (2S, 4S)-6-fluoro-2',
5'-dioxospiro [chroman-4, 4'-imidazolidine]-2-carboxamide which is used as an experimental example in the invention of a
25 prophylactic or therapeutic agent for diabetic maculopathy as claimed in claim 1. Accordingly, it is considered that the prior art documents contain no description that motivates the invention of claim 2 and that the invention of claim 2 has an

unexpected advantageous effect, as described in regard to claim 1.

(iii) The Invention of Claim 3 and Prior Art Documents

Claim 3 limits an intended disease to macular edema or
5 diabetic pigment epitheliopathy each of which is a specific
symptom of diabetic maculopathy in the invention of a
prophylactic or therapeutic agent for diabetic maculopathy as
claimed in claim 1 or 2. The macular edema is especially an
end-point in a pharmacological test. Accordingly, it is
10 considered that the prior art documents contain no description
that motivates the invention of claim 3 and that the invention
of claim 3 has an unexpected advantageous effect, as described
in regard to claim 1.

(iv) The Invention of Claim 4 and Prior Art Documents

15 Claim 4 limits the specific end-point in the diabetic
maculopathy in the invention of a prophylactic or therapeutic
agent for diabetic maculopathy as claimed in claim 1, to
improvement of visual acuity or inhibition of deterioration of
visual acuity in diabetic maculopathy. Accordingly, it is
20 considered that the prior art documents contain no description
that motivates the invention of claim 4 and that the invention
of claim 4 has an unexpected advantageous effect, as described
in regard to claim 1.

Additionally, it is considered to be an unexpected effect
25 that the compound not only ameliorates edema but also improves
visual acuity or prevents deterioration of visual acuity by
clinical investigation.

(v) The Invention of Claim 5 and Prior Art Documents

Original claim 4 has been changed to independent claim 5 so that the invention is recited more clearly. Accordingly, claim 5 conforms to claim 4.

(vi) The invention of Claim 6 and Prior Art Documents

5 Claim 6 limits the compound to (2S, 4S)-6-fluoro-2', 5'-dioxospiro [chroman-4, 4'-imidazolidine]-2-carboxamide which is used as an experimental example in the invention of a prophylactic or therapeutic agent for diabetic maculopathy as claimed in claim 5. Accordingly, claim 6 conforms to claim 5.

10 (vii) Conclusion

As obvious from the foregoing, the invention claimed in each of claims 1 to 6 is not described in the prior art documents, so it is not the invention under Patent Law Article 29 (1) (iii). Furthermore, the prior art documents contain no description that
15 motivates the invention claimed in each of claims 1 to 6 and the invention has an unexpected advantageous effect. Accordingly, it is not the invention under Patent Law Article 29(2). Consequently, the invention claimed in each of claims 1 to 6 is patentable under Patent Law Article 29(1), main paragraph.

20 (3) A Certificate of Experimental Results

Next, a certificate of experimental results carried out regarding the present invention will be explained. The experiment is composed of three tests of A. pharmacological preliminary test 1 using crab-eating monkeys, B. pharmacological
25 preliminary test 2 using crab-eating monkeys, and C. pharmacological test using crab-eating monkeys of experimental diabetes.

A. Pharmacological preliminary test 1 using crab-eating monkeys
-Epalrestat 400 mg/kg/day short-term repeated administration
test-

1. Purpose

5 The purpose of this test is to set a maximum effective dose
of epalrestat used in macular edema evaluation study with
streptozotocin (STZ) induced diabetic crab-eating monkey. The
toxic dose level of epalrestat in the dog 3-month sub-acute
toxicity test is estimated to be 500 mg/kg/day. A decreasing
10 trend of the body weight is perceived at a 22nd day of
administration by this dose¹⁾. Based on the foregoing report,
repeated administration of 400 mg/kg/day for 5 days was
determined.

15 2. Experimental material and method

2.1. Test article

Epalrestat (Lot No. EPA-06510, Sanyo Chemical Laboratory
Co., Ltd.) was employed as a test article.

2.2. Test method

20 2.2.1. Grouping

Four normal male crab-eating monkeys (Macaca
fascicularis) from Nafovanny, Vietnam, ranging from 2 and 3 years
old, were divided into two groups each of which was composed of
two.

25 1) Control group (two monkeys)

2) Epalrestat 400 mg/kg/day administrated group (two monkeys)

2.2.2. Medication administration and blood drawing

A catheter was inserted from the buccal cavity through the

esophagus into the stomach so that an epalrestat suspension (prepared by 5% gum arabic solution) was administered. Administration was carried out three times a day (in the morning, daytime and at night) and repeated for five days. A 5% gum arabic solution was orally administered to the control group in a ratio of 5 ml/kg. The general condition and body weight were monitored every day in the administration period. Furthermore, blood was drawn from the saphena immediately before administration and five days after the administration using a disposable syringe barrel and needle without use of an anesthetic. Drawn blood was put into a Venoject II (Terumo Corporation) and left for 40 to 60 minutes at a room temperature. A biochemical examination using obtained blood serum was entrusted to the Corporation for Production and Research of Laboratory Primates.

15

3. Experimental results

3.1. General condition

No significant changes in the condition were found in each individual of the control group during the test. In the test article administered group, excretion of test article color-like urine was found from a first to fifth administration days regarding each individual. One of the monkeys had about 2 mL vomit of test article-like substance five days after administration, and another monkey had about 3 mL vomit of test article-like substance four and five days after administration.

25

3.2. Body Weight

TABLE 1 shows body weight changes. No significant changes in the body weight were found in each individual of the control

group during the test. In the test article administered group, one of the monkeys had weight loss of 0.2 kg five days after administration, and another monkey had weight loss of 0.3 kg five days after administration. The monkey which had the weight loss
 5 of 0.2 kg during five days died five days after cessation of the test article.

3.3. Biochemical examination of blood serum

TABLE 2 shows results of the examination. No changes were found in the control group before and after the administration.
 10 In the test article administered group, changes were found in each of BUN, GPT, LDH, CRE and T-BIL.

4. Summary

400 mg/kg/day epalrestat was considered to be a toxic dose
 15 based on aggravation of general condition, weight loss and variations in hepatic and kidney damage markers.

5. Reference

- 1) Katsumasa ISHIMURA, Hitoshi OGAWA, Koichi ISOWA, Hidetoshi
 20 KASHIMA and Shinji WATANABE, et al., Three-Month Subacute Toxicity Test and One-Month Recovery Test in Dogs by Oral Administration of ONO-2235, Modern Medical Care (Gendai-Iryou), 1986; 18 (Supplement III); p. 162-231. (attached as document 5)

TABLE 1 CHANGE IN BODY WEIGHT

Group	Dose (mg/kg)	Animal	First day	Second day	Third day	Fourth day	Fifth. day
Control	0	(1)	2.4	2.3	2.3	2.3	2.3
		(2)	2.4	2.4	2.4	2.4	2.4

Epalrestat	400	(1)	2.5	2.5	2.5	2.5	2.3
		(2)	2.5	2.4	2.4	2.3	2.2

TABLE 2 BIOCHEMICAL EXAMINATION OF BLOOD SERUM

Group	Dose	Animal	BUN	GOT	GPT	ALP	LDH
	(mg/kg)		(mg/dL)	(IU/L)	(IU/L)	(IU/L)	(IU/L)
Control	0	(1) B	18.8	26	29	1717	244
		(2) B	23.8	21	16	2143	234
Epalrestat	400	(1) B	20.0	29	46	1934	270
		(2) B	22.1	31	38	2546	233
Control	0	(1) A	20.8	27	35	2009	289
		(2) A	27.8	25	21	2322	300
Epalrestat	400	(1) A	39.1	43	104	2138	778
		(2) A	26.0	38	48	1914	287

where "B" designates the value before administration and "A" designates the value after administration for five days; and where BUN designates blood urea nitrogen, GOT glutamic-oxaloacetic transaminase, GPT glutamic-pyruvic transaminase, ALP alkaline phosphatase, LDH lactate dehydrogenase, CRE Creatinine and T-BIL total bilirubin.

TABLE 2 BIOCHEMICAL EXAMINATION OF BLOOD SERUM -Continued-

Group	Dose	Animal	CRE	T-BIL
	(mg/kg)		(mg/dL)	(mg/dL)
Control	0	(1) B	0.5	0.2
		(2) B	0.6	0.4
Epalrestat	400	(1) B	0.4	0.2
		(2) B	0.5	0.2
Control	0	(1) A	0.5	0.2
		(2) A	0.5	0.3

Epalrestat 400	(1) A	1.5	0.4
	(2) A	1.1	0.7

B. Pharmacological preliminary test 2 using crab-eating monkeys

-Epalrestat 150 mg/kg/day short-term repeated administration

5 test-

1. Purpose

The purpose of this test is to set a maximum effective dose of epalrestat used in macular edema evaluation study with streptozotocin (STZ) induced diabetic crab-eating monkey. Since
 10 a toxic action was seen in the epalrestat 400 mg/kg/day short-term repeated administration test, inspection was carried out with the dose being reduced to 150 mg/kg/day.

2. Experimental material and method

15 2.1. Test article

Epalrestat (Lot No. EPA-06510, Sanyo Chemical Laboratory Co., Ltd.) was employed as a test article.

2.2. Test method

2.2.1. Grouping

20 Three normal male crab-eating monkeys (Macaca fascicularis) from Nafovanny, Vietnam, ranging from 2 and 3 years old, were used. Only one medication administration group was set in order that toxic action may be detected before and after administration.

25 1) Epalrestat 150 mg/kg/day administered group (three monkeys)

2.2.2. Medication administration and blood drawing

A catheter was inserted from the buccal cavity through the esophagus into the stomach so that an epalrestat suspension (prepared by 5% gum arabic solution) was administered. Administration was carried out three times a day (in the morning, 5 daytime and at night) and repeated for six days. The general condition and body weight were monitored every day in the administration period. Furthermore, blood was drawn from the saphena or femoral vein immediately before administration and 10 six days after the administration using a disposable syringe barrel and needle without use of an anesthetic. Drawn blood was put into a Venoject II (Terumo Corporation) and left for 40 to 60 minutes at a room temperature. A biochemical examination using obtained blood serum was entrusted to the Corporation for Production and Research of Laboratory Primates.

15

3. Experimental results

3.1. General condition

In all the individuals, excretion of test article color-like urine was found from a first to sixth administration 20 days.

3.2. Body Weight

TABLE 3 shows body weight changes. All the individuals had weight loss of 0.1 to 0.2 kg five or six days after administration.

25 3.3. Biochemical examination of blood serum

TABLE 4 shows results of the examination. By treatment with test article, changes were found in each of BUN, GPT, LDH and CRE.

4. Summary

Mild but temporal weight loss was seen and variations in hepatic and kidney damage markers were also seen, and accordingly, 150 mg/kg/day epalrestat was also considered to be a toxic dose.

TABLE 3 CHANGE IN BODY WEIGHT

Group	Dose (mg/kg)	Animal	First day	Second day	Third day	Fourth day	Fifth day	Sixth day
Epalrestat 150		(1)	2.3	2.3	2.2	2.2	2.1	2.1
		(2)	2.3	2.4	2.3	2.2	2.1	2.1
		(3)	2.4	2.4	2.4	2.4	2.3	2.3

TABLE 4 BIOCHEMICAL EXAMINATION OF BLOOD SERUM

Group	Dose (mg/kg)	Animal	BUN (mg/dL)	GOT (IU/L)	GPT (IU/L)	ALP (IU/L)	LDH (IU/L)
Epalrestat 150		(1) B	19.4	34	17	2782	266
		(2) B	19.4	36	30	1812	248
		(3) B	16.5	44	19	2186	366
		(1) A	46.6	57	139	2139	783
		(2) A	46.9	35	58	1421	575
		(3) A	15.7	27	17	2358	342

where "B" designates the value before administration and "A" designates the value after administration for six days; and where BUN designates blood urea nitrogen, GOT glutamic-oxaloacetic transaminase, GPT glutamic-pyruvic transaminase, ALP alkaline phosphatase, LDH lactate dehydrogenase, CRE Creatinine and T-BIL total bilirubin.

TABLE 4 BIOCHEMICAL EXAMINATION OF BLOOD SERUM -Continued-

Group	Dose (mg/kg)	Animal	CRE (mg/dL)	T-BIL (mg/dL)
Epalrestat 150		(1) B	0.5	0.2
		(2) B	0.5	0.2
		(3) B	0.5	0.2
		(1) A	4.9	0.2
		(2) A	2.9	0.1
		(3) A	0.9	0.2

C. Pharmacological study using experimental diabetic crab-eating monkeys

-Action of SNK-860 and epalrestat against macular edema due to ischemic reperfusion-

The effectiveness of aldose reductase inhibitor on macular edema due to ischemic reperfusion was compared regarding SNK-860 and epalrestat using streptozotocin (STZ) induced diabetic crab-eating monkeys (*Macaca fascicularis*).

10

2. Experimental material and method

2.1. Diabetes inducing substance and insulin

Diabetes mellitus was induced in monkeys by intravenously injecting streptozotocin (STZ: Lot No. 046K1206, Sigma) into their foreleg vein at the dose of 80 mg/kg. Insulin (NOVOLIN (registered trademark), NovoNordisk A/S) was administered subcutaneously twice a day (before feeding in the morning and in the evening). An applied dose of insulin was determined to be a slight amount necessary for subsistence (0.01 to 0.05

mL/body).

2.2. Test article

SNK-860 (Lot No. 901T-4) was employed as a test article. It is reported that SNK-860 suppresses 50% sorbitol accumulation at the dose of 2 mg/kg and 100% sorbitol accumulation at the dose of 16 mg/kg. Based on the report, the dose sufficiently suppressing sorbitol accumulation was set at 4 mg/kg/day and 8 mg/kg/day. Administration was carried out once a day (in the morning) for 14 days before increase in the intraocular pressure and for 7 days after increase in the intraocular pressure.

2.3. Control article

Epalrestat (Lot No. EPA-06510, Sanyo Chemical Laboratory Co., Ltd.) was employed as a control article. The dose was set at 25 mg/kg/day and 50 mg/kg/day based on the experiment results of preliminary test 1 and 2, and the report that 73% sorbitol accumulation was suppressed in the retina of a diabetic model at the dose of 50 mg/kg/day. Administration was carried out three times a day (in the morning, daytime and at night) for 14 days before increase in the intraocular pressure and for 7 days after increase in the intraocular pressure.

2.4. Test method

2.4.1. Grouping

STZ was administered to 20 male crab-eating monkeys (*Macaca fascicularis*) from Nafovanny, Vietnam, ranging from 2 and 3 years old, to induce diabetes mellitus. Surviving 16 monkeys were divided into four groups. The grouping was carried out three weeks after administration of STZ in view of glycated hemoglobin levels, body weight and results of general condition before

administration of medications (test article or control article).

Groups were as follows:

- 1) Diabetic control group (4 monkeys);
- 2) Diabetic group of given 4 mg/kg SNK-860 (3 monkeys);
- 5 3) Diabetic group of given 8 mg/kg SNK-860 (3 monkeys);
- 4) Diabetic group of given 25 mg/kg epalrestat (3 monkeys); and
- 5) Diabetic group of given 50 mg/kg epalrestat (3 monkeys).

2.4.2. Preparation of retinal ischemia by increase of the intraocular pressure

10 Intraocular pressure was applied to both eyes of each monkey at a 14th day of administration by the following method:

 A drip infusion set (Terufusion Drip Infusion Set manufactured by Terumo) was connected to a bottle containing an intraocular perfusion solution (Opeguard MA manufactured by
15 Senju Pharmaceutical Co., Ltd.), and an extension tube to which a three-way stopcock had been attached was connected thereto. A needle was fitted to the end of the tube. The bottle was fixed to a stand so that a liquid level of the intraocular perfusion solution is 184 cm high relative to monkey's eyes. A mydriatic
20 (Mydrin P manufactured by Santen Pharmaceutical Co., Ltd.) was dropped onto monkey's eye with sufficient mydriatic action. Thereafter, Ketalar (Sankyo Lifetech Co., Ltd.) was administered into muscle for anesthesia. Subsequently, a local anesthetic agent (Benoxyl eye drop 0.4%, Santen Pharmaceutical Co., Ltd.)
25 was dropped and a lid retractor was then attached to prevent blinking. Ketalar was timely added. Thereafter, a needle was stuck into an anterior chamber of the monkey's eye and the three-way stopcock was operated so that pressure is applied in

the eye, whereby a retina ischemic condition was prepared. An ischemic time by application of intraocular pressure was set to 60 minutes. After application of the intraocular pressure, the needle was removed to relieve the intraocular pressure to allow
5 reperfusion, and an antibacterial eye drop (tarivit eye ointment manufactured by Santen Pharmaceutical Co., Ltd.) was applied onto the eye. The thickness of macula was measured using an OCT scanner (Stratus OCT, Carl Zeiss Meditec AG) two days after application of intraocular pressure (16 days after medication
10 administration) and four days after application of intraocular pressure (18 days after medication administration). Evaluation was carried out without consideration of eyeballs to which insufficient intraocular pressure was applied and in which macula was not observed by the OCT scanner.

15 2.4.3. Measurement of macula thickness

Macula cross-sectional imaging of the monkey under anesthesia was photographed using an OCT scanner on a fourteenth day from medication administration (immediately before application of intraocular pressure), a sixteenth day (two days
20 after application of intraocular pressure) and eighteenth day (four days after application of intraocular pressure). Evaluation was carried out with respect to the minimum thickness of macula center.

2.4.4. Dissection

25 The monkeys were normally raised after application of intraocular pressure. Measurement of body weight and blood drawing were carried out 21 days after medication administration (seven days after application of intraocular pressure) and

thereafter, dissection was also carried out. Glycated hemoglobins were measured using drawn blood.

3. Test results

5 3.1. Effect on macular edema

TABLE 5 shows the results. A macular edema of diabetic monkey (an increase in the minimum thickness of macula center) was produced by application of intraocular pressure. The macular edema was seen during four days after application of
10 intraocular pressure. Significant edema suppressing effect was admitted in the diabetic monkeys to which 4 or 8 mg/kg/day SNK-860 was administered. On the other hand, no significant edema suppressing effect was admitted in the diabetic monkeys to which 25 or 50 mg/kg/day epalrestat was administered.

15 3.2. Effect on body weight and glycated hemoglobin

TABLE 6 shows the results. No difference was seen among groups regarding body weight and glycated hemoglobin. Furthermore, the weight and hemoglobin were increased in all groups as compared with the time of grouping.

20

4. Summary

1) SNK-860 exhibited stronger suppression of macular edema in diabetes mellitus than epalrestat.

2) No effect was seen even when the dose of epalrestat was
25 increased and accordingly, the effectiveness thereof against macular edema in diabetes mellitus was unclear. Additionally, the set dose (25 and 50 mg/kg/day) was considered to have no controversial toxic effect.

3) The level of hemoglobin was rendered larger at the time of final administration than at the time of grouping, regarding all groups. Accordingly, the medicinal effect was considered to be brought by each medication but not by a blood glucose improving effect of insulin.

5. Reference

1) IG Obrosova, AG Minchenko, R Vasupuram, L. White, OI Abatan, AK Kumagai, RN Frank and MJ Stevens, Aldose reductase inhibitor fidarestat prevents retinal oxidative stress and vascular endothelial growth factor overexpression in streptozotocin-diabetic rats. Diabetes 2003; 52: 864-871 (attached hereto as document 6).

2) N Hotta, H Kakuta, H Fukasawa, M Kimura, N Koh, M Iida, H Terashima, T Morimura and N Sakamoto, Effects of a fructose-rich diet and the aldose reductase inhibitor, ONO-2235, on the development of diabetic neuropathy in streptozotocin-treated rats, Diabetologia 1985; 28; 176-180 (attached hereto as document 7).

20

TABLE 5 MINIMUM THICKNESS OF MACULAR CENTER
AFTER APPLICATION OF INTRAOCULAR PRESSURE

25

Group	Dose (mg/kg)	Number of eyes	Before application of intraocular pressure
Diabetic control	-	7	135±3

SNK-860	4	5	128±5
	8	6	131±5
Epalrestat	25	4	130±6
	50	6	128±4

TABLE 5 MINIMUM THICKNESS OF MACULAR CENTER
AFTER APPLICATION OF INTRAOCULAR PRESSURE -Continued-

Group	Application of intraocular pressure	
	Two days after	Four days after
Diabetic control	182±15 #	152±6 #
SNK-860	139±10 *	135±8
	140±7 *	138±5
Epalrestat	164±22	152±9
	189±31	161±15

where average±standard error (μm), #p<0.05 versus before application of intraocular pressure, and *p<0.05 versus diabetic control.

TABLE 6 BODY WEIGHT AND GLYCATED HEMOGLOBIN

Group	Dose (mg/kg)	Number of monkeys	Body Weight (kg)	
			Grouping	Final
Diabetic control	-	4	2.2±0.1	2.4±0.2
SNK-860	4	3	2.3±0.4	2.4±0.4
	8	3	2.1±0.0	2.2±0.0
Epalrestat	25	3	2.2±0.2	2.3±0.1
	50	3	2.2±0.1	2.2±0.1

5 TABLE 6 BODY WEIGHT AND GLYCATED HEMOGLOBIN -Continued-

Group	Glycated hemoglobin (%)	
	Grouping	Final

Diabetic control	7.7±0.8	8.2±0.7
SNK-860	7.5±0.6	8.8±0.7
	8.0±0.2	9.2±0.2
Epalrestat	8.5±0.1	9.1±0.5
	7.9±1.8	8.8±1.8

where grouping designates "at the time of grouping" and final designates "at the time of final medication administration" and average±standard error

[List of filed articles]

[Name of article] Document 1: MA Speicher et al., Pharmacologic therapy for diabetic retinopathy, Expert Opinion on Emerging
5 Drugs 2003; 8; 239-250.

[Name of article] Document 2: M Akita et al., Effects of an aldose reductase inhibitor, SNK-860, on the histopathological changes of retinal tissues in a streptozotocin-induced diabetic rat model, Acta Med Okayama 1993; 47; 299-304.

10 [Name of article] Document 3: JP-A-H07-242547 (attachment is eliminated)

[Name of article] Document 4: Hidetoshi Yamashita and Ryo Kawasaki ed., Diabetic Retinopathy: Best Advice By Medical Specialist, Tokyo, Shindann-to-Chiryousha, 2003, pages 47-59.

15 [Name of article] Document 5: Katsumasa ISHIMURA, Hitoshi OGAWA, Koichi ISOWA, Hidetoshi KASHIMA and Shinji WATANABE, et al., Three-Month Subacute Toxicity Test and One-Month Recovery Test in Dogs by Oral Administration of ONO-2235, Modern Medical Care (Gendai-Iryou)., 1986; 18 (Supplement III); p. 162-231.

20 [Name of article] Document 6: IG Obrosova, AG Minchenko, R

Vasupuram, L. White, OI Abatan, AK Kumagai, RN Frank and MJ Stevens, Aldose reductase inhibitor fidarestat prevents retinal oxidative stress and vascular endothelial growth factor overexpression in streptozotocin-diabetic rats. Diabetes
5 2003; 52: 864-871.

[Name of article] Document 7: N Hotta, H Kakuta, H Fukasawa, M Kimura, N Koh, M Iida, H Terashima, T Morimura and N Sakamoto, Effects of a fructose-rich diet and the aldose reductase inhibitor, ONO-2235, on the development of diabetic neuropathy
10 in streptozotocin-treated rats, Diabetologia 1985; 28; 176-180.

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【早期審査に関する事情説明】

1. 事情

欧州特許庁、米国特許庁、中国特許庁、韓国特許庁、カナダ特許庁、及びオーストラリア特許庁へ出願を行った。

欧州特許庁への出願の出願番号は05704239. 2である。米国特許庁への出願の出願番号は10/587, 320である。中国特許庁への出願の出願番号は200580003659. 1である。韓国特許庁への出願の出願番号は10-2006-7015812である。カナダ特許庁への出願の出願番号は2554679である。オーストラリア特許庁への出願の出願番号は2005207906である。

2. 先行技術の開示及び対比説明

(1)文献名

本願の原出願である国際特許出願(PCT/JP2005/1187)の国際予備審査によれば、本願発明に関連する文献は以下のとおりである。

文献1. MA Speicher et al., Pharmacologic therapy for diabetic retinopathy, Expert

II (b)(i)

Opinion on Emerging Drugs 2003; 825239

文献2. M Akita et al Effects of aldose reductase inhibitor, SNK860, on the histopathological changes of retinal tissues in streptozotocin-induced diabetic rat model, Acta Med Okayama 1993; 47: 304299

文献3. 特開平7-242547号公報

(2) 対比説明

本願発明は、5月14日付にて提出した手続補正書によって、補正されております。

(i) 請求項1に記載の発明と先行技術文献

請求項1は、一般式[化1]で記載された化合物を有効成分とする糖尿病黄斑症の予防又は治療剤に係る発明です。この一般式で記載された化合物は、SNK-860として知られる(2S,4S)-6-フルオロ-2',5'-ジオキソスピロ[クロマン-4,4'-イミダゾリジン]-2-カルボキサミドを包含し、それに構造類似の化合物群です。

次に、先行技術文献について説明します。

文献1には、「増殖性糖尿病網膜症(PDR)及び黄斑浮腫(ME)は、血糖コントロールや各種糖代謝異常の改善(AR阻害剤、抗グリケーション剤、PKC阻害剤)により予防することができる可能性がある。」との記載がアブストラクトにあります。確かに、PKC阻害剤については、糖尿病網膜症及び黄斑浮腫に対して開発が進んでいて、有効性が確認されていることが述べられています。しかし、アルドース還元酵素阻害剤(AR阻害剤)については、黄斑浮腫に対する有効性について全く述べられていません。しかも、糖尿病網膜症においても、AR阻害剤は動物試験では有効性が見られるものの、臨床試験においては、有効性が見られない(特にソルビニル)との否定的な見解が示されています(p242の左側5~9行目)。

また、文献2、3ですが、ここには、実験動物モデルでの結果に基づいて、SNK-860が網膜における浮腫又は糖尿病性単純網膜症の改善に有効である旨、記載されています。

次にこれらの文献を読んだ当業者がどのような示唆を受けるかについて説明します。

前記文献1を読んだ当業者は、PKC阻害剤は糖尿病網膜症及び黄斑浮腫の改善に有効であるが、AR阻害剤は、糖尿病網膜症又は黄斑浮腫の改善に、臨床試験で有効性を示すのは難しいとの認識をもつものと考えられます。文献は、あくまで全部を読んでそこに何が記載されているかを判断すべきであり、部分的な記載、即ち、アブストラクトのみの記載

で判断するものではありません。当業者は、多くの AR 阻害剤が、糖尿病網膜症の動物実験では有効であったにもかかわらず、臨床試験で有効性が示されていないことを知っていますので、間違いなく、この結論に到達するはずです。

また、文献 1 と文献 2, 3 を組み合わせた場合、当業者は、SNK-860 についても、糖尿病性網膜症の実験動物モデルでは有効であるが、糖尿病性網膜症、糖尿病性黄斑症の臨床試験で有効性を示すのは難しいとの示唆を受けるはずです。即ち、SNK-860 を含む構造類似の化合物群についても、同様の示唆を受けることになります。

以上より、先行技術文献には、本願請求項 1 に記載の発明の動機付けとなり得る記載はないものと考えられます。

ここで出願人は、更に、本願請求項 1 に記載の発明が予測できない有利な効果を有することを実験データでもって示すことにします。

後述の実験成績証明書は、一般式[化 1]に記載された化合物の中で最も代表的な化合物である SNK-860 と、臨床試験で唯一、糖尿病性網膜症に対する有効性が確認されたエパルレスタットとを、糖尿病性黄斑症のサルの実験モデルで比較したものです。このデータからわかるように、エパルレスタットは、毒性が発現しない範囲で用量を上げてても効果は見られませんが、SNK-860 は、低用量で見事に黄斑浮腫を抑制しています。これは、全か無かの違いがある程の顕著な差であり、紛れもなく、予測できない有利な効果といえるものであります。

尚、糖尿病性黄斑症について再度説明させていただきますと、組織的にも黄斑と網膜は異なる形態を有しており、糖尿病性黄斑症と糖尿病性網膜症は、教科書的にも、全く異なる疾患として捉えられており、同一視できるものではありません(下記文献 4)。また、SNK-860 の糖尿病性黄斑症に対する有効性は、明細書記載の臨床試験でも確認されており、実験モデルでしか効かないというものではありません。

文献 4. 山下英俊, 川崎良編。糖尿病網膜症 専門医によるベストアドバイス。東京: 診断と治療社; 2003. p.4759.

(ii) 請求項 2 に記載の発明と先行技術文献

請求項 2 は、請求項 1 に係る糖尿病黄斑症の予防又は治療剤の発明において、化合物を実施例として使用されている(2S,4S)-6-フルオロ-2',5'-ジオキソスピロ[クロマン-4,4'-イミダゾリジン]-2-カルボキサミド (SNK-860) に限定したものです。ですから、先行技術文

献に、本願請求項 2 に記載の発明の動機付けとなる記載がないこと、及び、当該発明が予測できない有利な効果を有することは、請求項 1 に関連して述べたとおりです。

(iii) 請求項 3 に記載の発明と先行技術文献

請求項 3 は、請求項 1 又は 2 に係る糖尿病黄斑症の予防又は治療剤において、糖尿病黄斑症の具体的な症状である黄斑浮腫又は糖尿病色素上皮症に使用対象を限定したものです。黄斑浮腫は特に、薬理試験における評価項目ともなっているものです。ですから、先行技術文献に、本願請求項 3 に記載の発明の動機付けとなる記載がないこと、及び、当該発明が予測できない有利な効果を有することは、請求項 1 に関連して述べたとおりです。

(iv) 請求項 4 に記載の発明と先行技術文献

請求項 4 は、請求項 1 に係る糖尿病黄斑症の予防又は治療剤において、糖尿病黄斑症における具体的な評価項目を限定、即ち、視力の改善又は低下防止剤として使用されるという限定を加えたものです。ですから、先行技術文献に、本願請求項 3 に記載の発明の動機付けとなる記載がないこと、及び、当該発明が予測できない有利な効果を有することは、請求項 1 に関連して述べたとおりです。

尚、単に浮腫改善をするだけでなく、より直接的に視力の改善又は低下防止効果を臨床試験で証明したところは、予測できない効果と言えるものと考えます。

(v) 請求項 5 に記載の発明と先行技術文献

請求項 5 は、文言をすっきりさせるために、請求項 4 を独立クレーム化したものです。ですから、請求項 4 に準じます。

(vi) 請求項 6 に記載の発明と先行技術文献

請求項 6 は、請求項 5 の発明において、化合物を実施例として使用されている(2S,4S)-6-フルオロ・2',5'-ジオキソスピロ[クロマン-4,4'-イミダゾリジン]-2-カルボキサミド(SNK-860)に限定したものです。ですから、請求項 5 に準じます。

(vii) 結論

上記の通りであり、本願の請求項 1～6 に係る各発明は、先行技術文献に記載されていませんので、特許法第 29 条第 1 項第 3 号に該当する発明ではありません。また更に、本願の請求項 1～6 に係る各発明は、先行技術文献には動機付けとなり得る記載はなく、しかも、予測できない有利な効果を奏しますので、特許法第 29 条第 2 項に該当する発明でもありません。従って、特許法第 29 条第 1 項柱書きの規定により特許を受けることがで

きる発明に該当するものです。

(3) 実験成績証明書

次に、本発明に関して行った実験成績証明を説明する。実験は、A. カニクイザルを用いた薬効薬理予備試験1、B. カニクイザルを用いた薬効薬理予備試験2、及びC. 実験的糖尿病カニクイザルを用いた薬効薬理試験の三種類から構成されている。

A. カニクイザルを用いた薬効薬理予備試験1

ーエパルレスタット 400 mg/kg/day 短期連投試験ー

1. 目的

streptozotocin(STZ)誘発糖尿病カニクイザル黄斑浮腫評価試験に用いるエパルレスタットの最大有効用量を設定する。尚、イヌ3ヶ月亜急性毒性試験におけるエパルレスタットの確実中毒量は500 mg/kg/dayと推察され、この用量では投与22日目より体重の減少傾向が認められている¹⁾。以上の報告から今回、400 mg/kg/dayの5日間投与とした。

2. 実験材料及び実験方法

2.1. 被験物質

エパルレスタット (Lot NoEPA-06510, 三洋化学研究所) を被験物質とした。

2.2. 実験方法

2.2.1. 群分け

2～3歳の健常雄性カニクイザル (ベトナム NAFOVANNY 産) 4頭を2頭ずつ以下の2群に分けた。

1) 対照群 (2頭)

2) エパルレスタット 400 mg/kg/day投与群 (2頭)

2.2.2. 薬物投与及び採血

カテーテルを口腔より食道を経て胃内に挿入し、エパルレスタット投与液 (5%アラビアゴム溶液で調製) を投与した。投与期間は5日間とし、1日3回に分けて投与した (朝、昼、夜)。尚、対照群には5%アラビアゴム溶液を5 mL/kgの割合で経口投与した。一般状態の観察及び体重測定は投与期間中毎日行った。また血液は無麻酔で、ディスポーザブル注射筒及び針を用いて、投与直前及び投与5日後に伏在静脈から採取した。得られた血液をベ

ノジェクトⅡ（テルモ）に入れ 40～60 分室温で放置した。得られた血清を用いての生化学検査は予防衛生協会に委託して行った。

3. 実験結果

3.1. 一般状態

対照群では、試験期間中、各個体において、特記すべき一般状態の変化はみられなかった。被験物質投与群では、各個体とも投与 1 日後から 5 日後まで「被験物質様色調の尿排泄」がみられた。1 頭は投与 5 日後に「被験物質様物質の嘔吐、約 2 mL」を、別の 1 頭は投与 4 日後及び 5 日後に「被験物質様物質の嘔吐、約 3 mL」を示した。

3.2. 体重

体重の推移を表 1 に示す。対照群では、試験期間中、各個体において、特記すべき体重の変化は認められなかった。被験物質投与群では、1 頭が投与 5 日後に 0.2kg の減少を、別の 1 頭が投与 5 日後に 0.3kg の減少を示した。尚、5 日間で 0.2kg 体重が減少した個体は休薬 5 日後に死亡した。

3.3. 血清生化学的検査

結果を表 2 に示す。対照群では、投与前後での変動は認められなかった。被験物質投与群では、BUN, GPT, LDH, CRP, T-BIL で変化が認められた。

4. まとめ

一般状態の悪化、体重減少及び肝障害腎障害マーカーの変動から、エパルレスタット 400 mg/kg/day は毒性用量と考えられた。

5. 参考文献

- 1) 石村勝正, 小川 仁, 磯和弘一, 鹿島秀敏, 渡辺進二他. ONO-2235 の経口投与におけるイヌでの 3 ヶ月亜急性毒性試験および 1 ヶ月回復試験. 現代医療 1986; 18 (増 III): 162-231. (文献 5 として添付)

【表1】

表1 体重の推移

群	用量 (mg/kg)	動物	1日目	2日目	3日目	4日目	5日目
対照	0	①	2.4	2.3	2.3	2.3	2.3
		②	2.4	2.4	2.4	2.4	2.4
エバルレスタット	500	①	2.5	2.5	2.5	2.5	2.5
		②	2.5	2.4	2.4	2.3	2.2

(kg)

【表2】

表2 血清学的検査

群	用量 (mg/kg)	動物	BUN (mg/dL)	GOT (IU/L)	GPT (IU/L)	ALP (IU/L)	LDH (IU/L)	CRE (mg/dL)	T-BIL (mg/dL)
対照	0	①前	18.8	26	29	1717	241	0.5	0.2
		②前	23.8	28	16	2143	234	0.6	0.4
エバルレスタット	400	①前	20.0	39	46	1924	270	0.4	0.2
		②前	22.1	31	38	2546	231	0.5	0.2
対照	0	①後	20.8	27	33	2009	289	0.5	0.2
		②後	27.8	25	31	2322	300	0.5	0.3
エバルレスタット	400	①後	39.1	43	104	2156	778	1.5	0.4
		②後	36.0	38	48	1914	287	1.3	0.7

“前”は投与前の値を示し、“後”は5日間の投与後の値を示す。

BUN:尿素窒素, GOT:グルタミン酸オキサロ酢酸トランスアミナーゼ

GPT:グルタミン酸ピルビン酸トランスアミナーゼ, ALP:アルカリホスファターゼ

LDH:乳酸脱水素酵素, CRE:クレアチニン, T-BIL:総ビリルビン

【表1】

表1 体重の推移

群	用量 (mg/kg)	動物	1日目	2日目	3日目	4日目	5日目
対照	0	①	2.4	2.3	2.3	2.3	2.3
		②	2.4	2.4	2.4	2.4	2.4
エバルレスタット	400	①	2.5	2.5	2.5	2.5	2.5
		②	2.5	2.4	2.4	2.3	2.2

(kg)

【表2】

表2 血清学的検査

群	用量 (mg/kg)	動物	BUN (mg/dL)	GOT (IU/L)	GPT (IU/L)	ALP (IU/L)	LDH (IU/L)	CRE (mg/dL)	T-BIL (mg/dL)
対照	0	①前	18.8	26	29	1717	241	0.5	0.2
		②前	23.8	21	16	2143	234	0.6	0.4
エバルレスタット	400	①前	20.0	39	46	1954	270	0.4	0.2
		②前	22.1	31	38	2546	251	0.5	0.2
対照	0	①後	20.8	27	35	2009	289	0.5	0.2
		②後	27.8	25	31	2322	300	0.5	0.3
エバルレスタット	400	①後	39.1	43	104	2158	778	1.5	0.4
		②後	36.0	38	48	1914	287	1.5	0.7

“前”は投与前の値を示し、“後”は5日間の投与後の値を示す。

BUN:尿素窒素, GOT:グルタミン酸オキサロ酢酸トランスアミナーゼ

GPT:グルタミン酸ピルビン酸トランスアミナーゼ, ALP:アルカリホスファターゼ

LDH:乳酸脱氢酵素, CRE:クレアチニン, T-BIL:総ビリルビン

B. カニクイザルを用いた薬効薬理予備試験 2

ーエパルレスタット 150 mg/kg/day 短期連投試験ー

1. 目的

streptozotocin(STZ)誘発糖尿病カニクイザル黄斑浮腫評価試験に用いるエパルレスタットの最大有効用量を設定する。尚、エパルレスタット 400 mg/kg/day短期連投試験において毒性作用がみられた為、用量を 150 mg/kg/dayに下げて検討した。

2. 実験材料及び実験方法

2.1. 被験物質

エパルレスタット (Lot NoEPA-06510, 三洋化学研究所) を被験物質とした。

2.2. 実験方法

2.2.1. 群分け

2～3 歳の健常雄性カニクイザル (ベトナム NAFOVANNY 産) 3 頭を使用した。薬物投与前後で影響を検討する為、今回薬物投与群 1 群のみとした。

1) エパルレスタット 150 mg/kg/day投与群 (3 頭)

2.2.2. 薬物投与及び採血

カテーテルを口腔より食道を経て胃内に挿入し、エパルレスタット投与液 (5%アラビアゴム溶液で調製) を投与した。投与期間は 6 日間とし、1 日 3 回に分けて投与した (朝、昼、夜)。一般状態の観察及び体重の測定は投与期間中毎日行った。また血液は無麻酔で、ディスプレイザブル注射筒及び針を用いて、投与直前及び投与 5 日後に伏在静脈もしくは大腿静脈から採取した。得られた血液をベノジェクト II (テルモ) に入れ 40～60 分室温で放置した。得られた血清を用いての生化学検査は予防衛生協会に委託して行った。

3. 実験結果

3.1. 一般状態

全ての個体において、投与 1 日後から 6 日後まで「被験物質様色調の尿排泄」がみられた。

3.2. 体重

体重の推移を表 3 に示す。全ての個体において、投与 5 日後から 6 日後に 0.1～0.2kg

の減少がみられた。

3.3. 血清生化学的検査

結果を表4に示す。被験物質投与によって、BUN、GPT、LDH及びCREで変化が認められた。

4. まとめ

軽度ではあるが経時的な体重減少がみられ、また肝障害腎障害マーカーの変動もみられたことから、150 mg/kg/dayの用量も毒性用量と考えられた。

【表3】

表3 体重の推移

群	用量 (mg/kg)	動物	1日目	2日目	3日目	4日目	5日目	6日目
エブリレスタット	150	①	23	23	22	22	21	21
		②	23	24	23	22	21	21
		③	24	24	24	24	23	23

(kg)

【表4】

表4 血清生化学的検査

群	用量 (mg/kg)	動物	BUN (mg/dL)	GOT (IU/L)	GPT (IU/L)	ALP (IU/L)	LDH (IU/L)	CRE (mg/dL)	T-BIL (mg/dL)
エブリレスタット	150	①前	19.4	34	17	2782	366	0.5	0.2
		②前	19.4	36	30	1812	343	0.5	0.3
		③前	16.5	44	19	2136	356	0.5	0.2
		①後	46.6	57	139	2130	783	4.9	0.2
		②後	46.0	35	53	1421	575	2.9	0.1
		③後	15.7	27	17	2158	342	0.9	0.2

*前は投与前の値を示し、*後は24時間の投与後の値を示す。

BUN: 尿素窒素, GOT: グルタミン酸オキサロ酢酸トランスアミナーゼ

GPT: グルタミン酸ピルビン酸トランスアミナーゼ, ALP: アルカリホスファターゼ

LDH: 乳酸脱氢酵素, CRE: クレアチニン, T-BIL: 総ビリルビン

C. 実験的糖尿病カニクイザルを用いた薬効薬理試験

—SNK-860 及びエパルレスタットの虚血再灌流による黄斑浮腫に対する作用—

1. 目的

streptozotocin(STZ)誘発糖尿病カニクイザルの網膜に虚血再灌流処理を施して、黄斑に浮腫を発現させた糖尿病黄斑症モデルを用いて、アルドース還元酵素阻害剤の有効性をSNK-860 及びエパルレスタットについて比較検討した。

2. 実験材料及び実験方法

2.1. 糖尿病惹起物質及びインスリン

糖尿病はstreptozotocin (STZ: Lot No. 046K1206, Sigma)を前肢橈側皮静脈より80 mg/kgの用量で投与して惹起した。STZ 投与翌日から剖検前日まで、血糖値が250 mg/dL 以上を示した場合、インスリン(ノボリン(登録商標) 30R 注 100, ノボノルディスクファーマ)を皮下注射した(原則1日2回(朝:給餌直前, 夕)。尚、インスリンの投与量は生存させる為に必要な少量(0.01~0.05 mL/body)とした。

2.2. 被験物質

SNK-860(Lot No. 901T-4)を被験物質とした。SNK-860は糖尿病モデルでの網膜中ソルビトール蓄積を2 mg/kg で50%抑制し、16 mg/kg で100%抑制することが報告されている¹⁾。この報告からソルビトール蓄積を充分抑制する用量として、4 mg/kg/day 及び8 mg/kg/dayを設定した。尚、投与は1日1回(朝)とし、眼圧負荷前14日間及び眼圧負荷後7日間行った。

2.3. 対照物質

エパルレスタット (Lot No. EPA-06510, 三洋化学研究所)を対照物質とした。用量は予備試験1及び2の成績及び50 mg/kgの用量で糖尿病モデルでの網膜中ソルビトール蓄積を73%抑制するという報告²⁾を基に、25 mg/kg/day 及び50 mg/kg/dayを設定した。尚、投与は臨床用法に準じ1日量を3回に分けて、朝、昼及び夜に行い、眼圧負荷前14日間及び眼圧負荷後7日間行った。

2.4. 実験方法

2.4.1. 群分け

2~3歳の雄性カニクイザル(ベトナム NAFOVANNY 産)20頭にSTZを投与して糖尿病を惹

起した。糖尿病惹起後、生存した 16 頭を群分けした。群分けは薬物（被験物質又は対照物質）投与前のグリコヘモグロビン値、体重値及び一般状態の結果を考慮して STZ 投与 3 週後に行った。群分けは以下の通りとした。

- 1) 糖尿病対照群 (4 頭)
- 2) SNK-860 4 mg/kg 投与糖尿病群 (3 頭)
- 3) SNK-860 8 mg/kg 投与糖尿病群 (3 頭)
- 4) エパルレスタット 25 mg/kg 投与糖尿病群 (3 頭)
- 5) エパルレスタット 50 mg/kg 投与糖尿病群 (3 頭)

2.4.2. 眼圧負荷による網膜虚血の作製

薬物投与開始 14 日目に各サルの両眼に眼圧負荷を行った。眼圧負荷の方法は以下の通りである。

眼内灌流液（オペガード MA, 千寿製薬）の入ったボトルに輸液セット（テルフュージョン輸液セット）を接続し、それに三方活栓を付けた延長チューブ（エクステンションチューブ）を接続した。チューブの先端には注射針を装着した。眼内灌流液の入ったボトルの水面がサルの目の位置から 184 cm の高さになるようにボトルをスタンドに固定した。サル眼に散瞳薬（ミドリン P, 参天製薬）を滴下し十分に散瞳した後、ケタラール（三共ライフテック）を筋肉内に投与して麻酔した。続いて局所麻酔薬（ベノキシール点眼液 0.4%, 参天製薬）を点眼し、開瞼器をつけて瞬きをしないようにした。ケタラールは適時追加した。その後サルの前眼房に注射針を刺入し、三方活栓を操作して眼内に圧力を負荷し網膜虚血状態を作製した。眼圧負荷による虚血時間は 60 分間とした。眼圧負荷後、注射針を抜いて眼圧負荷を解除するとともに再灌流を行い、抗菌剤（タリビット眼軟膏, 参天製薬）を眼に充分塗布した。眼圧負荷 2 日（薬物投与 16 日）後及び 4 日（薬物投与 18 日）後に黄斑部の厚さを OCT スキャナー（Stratus OCT: カールツァイスメディテック）を用いて測定した。眼圧負荷が充分でなかった眼球及び OCT スキャナーで黄斑観察ができなかった眼球は評価から外した。

2.4.3. 黄斑部の厚さの測定

薬物投与開始 14 日目（眼圧負荷直前）、16 日目（眼圧負荷 2 日後）、18 日目（眼圧負荷 4 日後）に、麻酔下で OCT スキャナーを用いてサルの黄斑断層像を撮影した。評価は黄斑中心の最小厚について行った。

2.4.4. 解剖

サルは眼圧負荷後、通常飼育を行った。薬物投与開始 21 日後（眼圧負荷 7 日後）に体重測定及び採血を行った後、解剖した。採血した血液を用いて、グリコヘモグロビン測定を行った。

3. 実験結果

3.1. 黄斑浮腫に対する作用

結果を表 5 に示す。眼圧負荷により糖尿病サルの黄斑浮腫（黄斑中心の最小厚の肥厚）が確認され、この浮腫は眼圧負荷 4 日後までみられた。SNK-860 4 mg/kg/day 又は 8 mg/kg/day を投与した糖尿病サルでは有意な浮腫抑制作用が認められた。一方、エパルレストアット 25 mg/kg/day 又は 50 mg/kg/day を投与した糖尿病サルでは有意な浮腫抑制作用は認められなかった。

3.2. 体重及びグリコヘモグロビンに対する作用

結果を表 6 に示す。体重及びグリコヘモグロビンは群間に差がみられなかった。また、全群、群分け時より体重が増加し、ヘモグロビン値も増加した。

4. まとめ

- 1) SNK-860 はエパルレストアットに比して、糖尿病時の黄斑浮腫発現に対して強い抑制作用を示した。
- 2) エパルレストアットは、用量を上げても見られず、糖尿病時の黄斑浮腫に対する有効性は明らかではなかった。尚、今回の設定用量（25 mg/kg/day, 50 mg/kg/day）では、問題となる毒性作用は無いと考えられた。
- 3) 全群、群分け時より最終投与時でグリコヘモグロビン値が増加していた。このことから、今回の薬効は各薬物によるものであり、インスリンの血糖改善作用によるものでないと考えられた。

5. 参考文献

- 1) IG Obrosova, AG Minchenko, R Vasupuram, L White, OI Abatan, AK Kumagai, RN Frank, MJ Stevens. Aldose reductase inhibitor fidarestat prevents retinal oxidative stress

and vascular endothelial growth factor overexpression in streptozotocin-diabetic rats. Diabetes 2003; 52: 864-871. (文献6として添付)

2) N Hotta, H Kakuta, H Fukasawa, M Kimura, N Koh, M Iida, H Terashima, T Morimura, N Sakamoto. Effects of a fructose-rich diet and the aldose reductase inhibitor, ONO-2235, on the development of diabetic neuropathy in streptozotocin-treated rats. Diabetologia 1985; 28: 176-180. (文献7として添付)

【表5】

表5 眼圧負荷後の黄斑中心の最小厚

群	用量 (mg/kg)	頭数	眼圧負荷前	眼圧負荷	
				2日後	4日後
糖尿病対照	—	7	135±3	182±25 [#]	152±6 [#]
SNK-800	4	5	128±5	139±10	155±8
	8	6	131±5	140±7	156±5
エパルレスタット	25	4	130±6	164±22	152±9
	50	6	128±4	139±11	161±15

平均値±標準偏差 (μm). [#] p<0.05 対眼圧負荷前. ^{*} p<0.05 対糖尿病対照

【表6】

表6 体重及びグリコヘモグロビン

群	用量 (mg/kg)	頭数	体重 (kg)		グリコヘモグロビン (%)	
			開始時	最終	開始時	最終
糖尿病対照	—	4	2.2±0.1	2.4±0.2	7.7±0.8	8.1±0.7
SNK-800	4	5	2.3±0.4	2.4±0.3	7.5±0.6	8.3±0.7
	8	5	2.1±0.0	2.2±0.0	8.0±0.2	9.2±0.2
エパルレスタット	25	5	2.2±0.3	2.3±0.1	6.3±0.1	9.1±0.5
	50	5	2.2±0.1	2.3±0.1	7.9±1.8	8.8±1.8

開始時: 開始時 最終: 最終
平均±標準偏差

【提出物件の目録】

【物件名】 文献1. MA Speicher et al, Pharmacologic therapy for diabetic retinopathy, Expert Opinion on Emerging Drugs 2003; 8:239 1

【物件名】 文献2. M Akita et al, Effects of an aldose reductase inhibitor, SNK on the pathological changes of retinal tissues in a streptozotocin-induced diabetic rat model, Acta Med Okayama 1993; 47:299 1

【物件名】 文献3. 特開平7-242547号公報 (添付を省略する)

【物件名】 文献4. 山下英俊, 川崎良編。糖尿病網膜症 専門医によるベストアドバイス。東京: 診断と治療社; 2003. p.479. 1

【物件名】 文献5. 石村勝正, 小川 仁, 磯和弘一, 鹿島秀敏, 渡辺進二他. ONO-2235 の経口投与におけるイヌでの3ヵ月亜急性毒性試験および1ヵ月回復試験. 現代医療 1986; 18 (増III): 162-231. 1

【物件名】 文献6. IG Obrosova, AG Minchenko, R Vasupuram, L White, OI Abatan, AK Kumagai, RN Frank, MJ Stevens. Aldose reductase inhibitor fidarestat prevents retinal oxidative stress and vascular endothelial growth factor overexpression in streptozotocin-diabetic rats. Diabetes 2003; 52: 864-871. 1

【物件名】 文献7. N Hotta, H Kakuta, H Fukasawa, M Kimura, N Koh, M Iida, H Terashima, T Morimura, N Sakamoto. Effects of auctose-rich diet and the aldose reductase inhibitor, ONO-2235, on the development of diabetic neuropathy in streptozotocin-treated rats. Diabetologia 1998; 41: 176-180. 1

(English translation)

Reference: Dispatch No. 348188 Dispatch Date:18/07/2007

NOTIFICATION OF REASONS FOR REFUSAL

Patent Application No. Patent Application No. 2005-517502
Drafting Date 10th July 2007
Examiner of JPO Hirofumi TOUMA, Serial No. 3543-4C00
Representative of Applicant Yohei KOBAYASHI
Applied Provision Patent Law Section 36

This application should be refused for the reason mentioned below. If the applicant has any argument against the reason, such argument should be submitted within 60 days from the date on which this notification was dispatched.

Reason

Reason 1:

Claims 1 and 3 to 5

Notes:

The definition of each substituent group in claims 1 and 5 contains the description of an optionally substituted C1 to C6 alkyl group. But by what range of functional group C1-6 alkyl group may be replaced is not definitely specified.

<Claims for which a reason for refusal has not been found>

No reason for refusal has been found regarding the invention claimed in each of claims 2 and 6. A new reason for refusal will be notified when having been found.

(*) Please note that no new matter must be added to when you file amendment. Furthermore, on this occasion, it is recommended that the part of the specification or drawings that supports amendment is clearly indicated in remarks.

Record of Result of Prior Art Document Search

Searched Fields IPC C07D491/107,

A61K 31/33 to 33/44,
A61P 27/02,

Data Base Name CAPLUS (STN),
CAOLD (STN),
REGISTRY (STN),
MEDLINE (STN),
BIOSIS (STN),
EMBASE (STN),
WPIDS (STN)

- Prior art documents
1. SPEICHER M.A. et al., Expert Opinion on Emerging Drugs 2003, Vol. 8/No. 1, p. 239-250.;
 2. Akita, Met al., Acta. Med. Okayama, 1993, Vol. 47/No. 5, p.299-304;
 3. JP-A-H07-242547;
 4. GIANNOUKAKIS, N., Current Opinion in Investigational Drugs, 2003, Vol.4/No.10, p1233-1239; and
 5. FERRIS, III, F.L., Survey of Ophthalmology, 2002, vol47/Suppl. 2, p. S237.

This record is not a component(s) of the reason(s) for refusal.

Please contact the following when you have any inquiry about the contents of this notification of reason for refusal or when you would like to conduct a personal interview:

Hirofumi TOUMA, 3rd Examination Department, Patent Office
Telephone 03-3581-1101 (Extension 3490)
Facsimile 03-3581-1342

A61K 31/33 to 33/44,
A61P 27/02,

Data Base Name CAPLUS (STN),
CAOLD (STN),
REGISTRY (STN),
MEDLINE (STN),
BIOSIS (STN),
EMBASE (STN),
WPIDS (STN)

- Prior art documents
1. SPEICHER M.A. et al., Expert Opinion on Emerging Drugs 2003, Vol. 8/No. 1, p. 239-250.;
 2. Akita, M et al., Acta. Med. Okayama, 1993, Vol. 47/No. 5, p.299-304;
 3. JP-A-H07-242547;
 4. GIANNOUKAKIS, N., Current Opinion in Investigational Drugs, 2003, Vol.4/No.10, p1233-1239; and
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This record is not a component(s) of the reason(s) for refusal.

Please contact the following when you have any inquiry about the contents of this notification of reason for refusal or when you would like to conduct a personal interview:

Hirofumi TOUMA, 3rd Examination Department, Patent Office
Telephone 03-3581-1101 (Extension 3490)
Facsimile 03-3581-1342

整理番号: 発送番号:348188 発送日:平成19年 7月18日

拒絶理由通知書

特許出願の番号 特願2005-517502
起案日 平成19年 7月10日
特許庁審査官 當麻 博文 3543 4C00
特許出願人代理人 小林 洋平 様
適用条文 第36条



この出願は、次の理由によって拒絶をすべきものである。これについて意見があれば、この通知書の発送の日から60日以内に意見書を提出して下さい。

理 由

1. この出願は、特許請求の範囲の記載が下記の点で、特許法第36条第6項第2号に規定する要件を満たしていない。

記

- ・理由 1
- ・請求項 1, 3~5
- ・備考

請求項1, 5における各置換基の定義において、「置換されていてもよいC1-6アルキル基」なる記載があるが、具体的にどのような範囲の官能基で置換されていてもよいのか、その範囲が明確に規定されているとはいえない。

<拒絶の理由を発見しない請求項>

請求項2, 6に係る発明については、現時点では、拒絶の理由を発見しない。拒絶の理由が新たに発見された場合には拒絶の理由が通知される。

(*) 補正をするときは、新規事項の追加にならないよう留意されたい。また、その際、補正の根拠となる明細書又は図面中の該当記載箇所について意見書中で明示されることが望ましい。

先行技術文献調査結果の記録

- ・調査した分野 IPC C07D491/107,
A61K 31/33~33/44,
A61P 27/02,

I(a)(i)

整理番号: 発送番号:348188 発送日:平成19年 7月18日 2/E

DB名 CAPLUS (STN) ,
CAOLD (STN) ,
REGISTRY (STN) ,
MEDLINE (STN) ,
BIOSIS (STN) ,
EMBASE (STN) ,
WPIDS (STN)

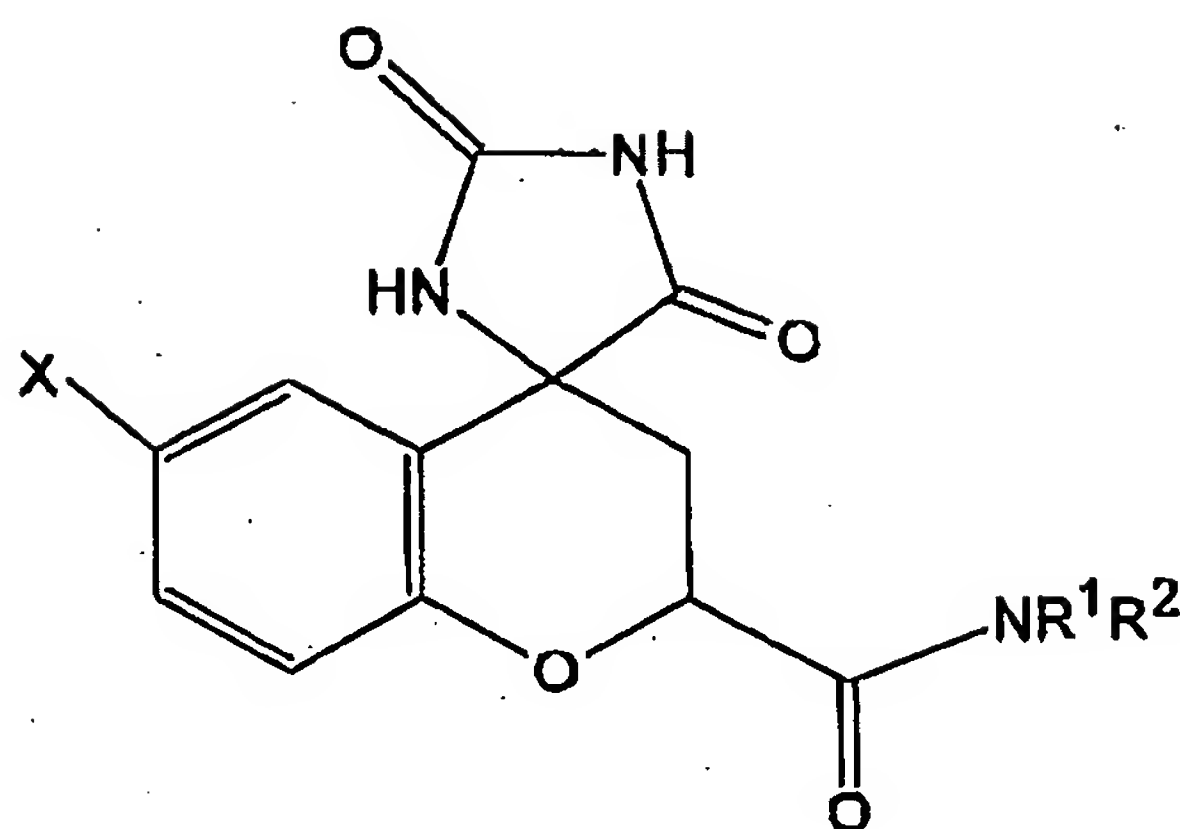
- ・先行技術文献
1. SPEICHER, M.A. et al., Expert Opinion on Emerging Drugs, 2003年, Vol.8/No.1, p.239-250
 2. AKITA, M. et al., Acta. Med. Okayama, 1993年, Vol.47/No.5, p.299-304
 3. 特開平7-242547号公報
 4. GIANNOUKAKIS, N., Current Opinion in Investigational Drugs, 2003年, Vol.4/No.10, p.1233-1239
 5. FERRIS, III, F.L., Survey of Ophthalmology, 2002年, Vol.47/Suppl.2, p.S237

この先行技術文献調査結果の記録は、拒絶理由を構成するものではない。

この拒絶理由通知の内容に関するお問い合わせ、または面接のご希望がございましたら下記までご連絡下さい。

特許審査第三部 医療 苗麻(とうま) 博文
TEL. 03 (3581) 1101 内線3490
FAX. 03 (3581) 1342

[Document Name] AMENDMENT
[Reference] P06023SKK
[Filing Date] 3rd August 2007
[Address] To the Commissioner, Patent Office
5 [Case Identification]
[Application Number] Patent Application No. 2005-517502
[Amender]
[Identification Number] 000144577
[Name] SANWA KAGAKU KENKYUSHO CO., LTD.
10 [Agent]
[Identification Number] 100108280
[Patent Attorney]
[Name] KOBAYASHI Youhei
[Telephone] 0594-27-5515
15 [Amendment 1]
[Amended Document] CLAIMS
[Amended Item] Whole Document
[Amending Method] Modification
[Amendment Contents]
20 [Document Name] CLAIMS
[Claim 1]
A prophylactic or therapeutic agent for diabetic
maculopathy, comprising, as an active ingredient, a compound
represented by the general formula:
25 [Chemical Formula 1]



(wherein X represents a halogen or a hydrogen atom, R¹ and R² concurrently or differently represent a hydrogen atom or a C1 to C6 alkyl group, or R¹ and R² together with a nitrogen atom
5 bound thereto and optionally another nitrogen atom or an oxygen atom, are combined to form a 5- to 6-membered heterocycle).

[Claim 2] The prophylactic or therapeutic agent for diabetic maculopathy according to claim 1, wherein the compound is (2S, 4S)-6-fluoro-2', 5'-dioxospiro
10 [chroman-4, 4'-imidazolidine]-2-carboxamide.

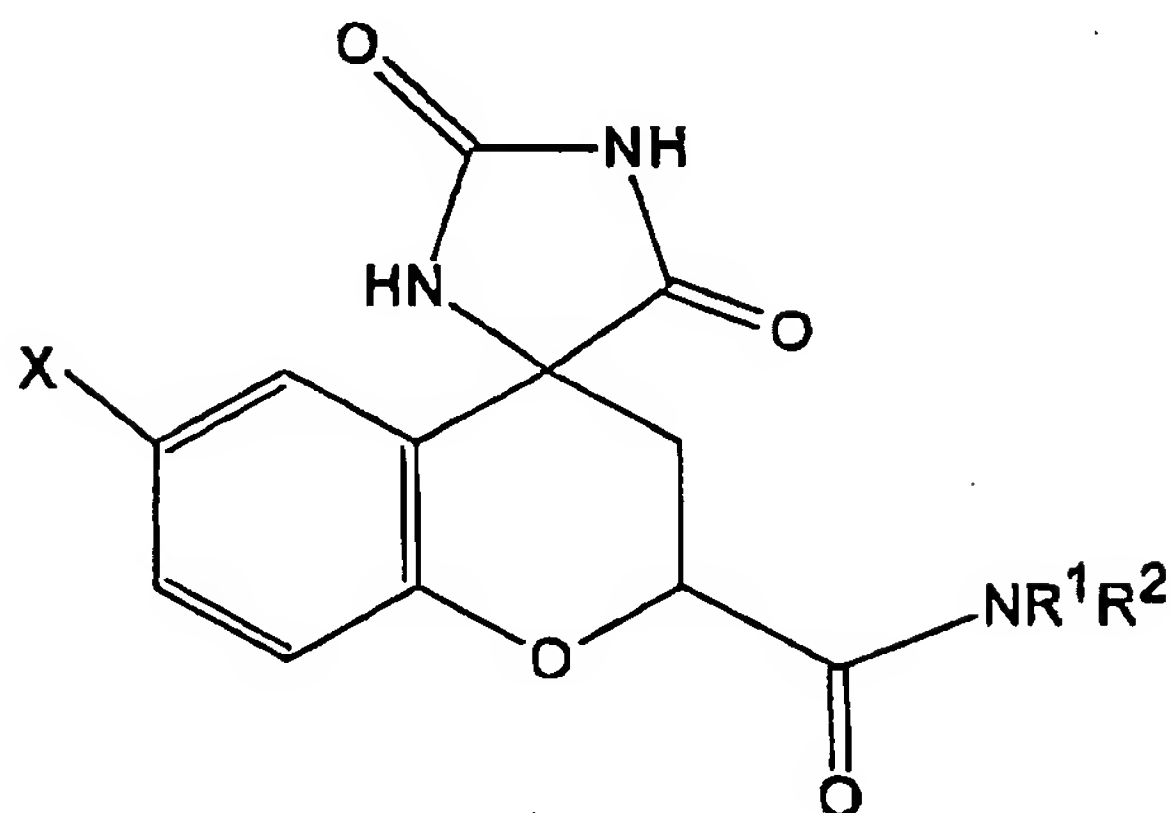
[Claim 3] The prophylactic or therapeutic agent for diabetic maculopathy according to claim 1 or 2, which is for use in macular edema or in retinal pigment epitheliopathy in diabetic maculopathy.

15 [Claim 4] The prophylactic or therapeutic agent for diabetic maculopathy according to claim 1 or 2, which is for use as an agent for improving visual acuity or inhibiting deterioration of visual acuity in diabetic maculopathy.

[Claim 5] An agent for improving visual acuity or inhibiting
20 deterioration of visual acuity in diabetic maculopathy,

comprising, as an active ingredient, a compound represented by the general formula:

[Chemical Formula]



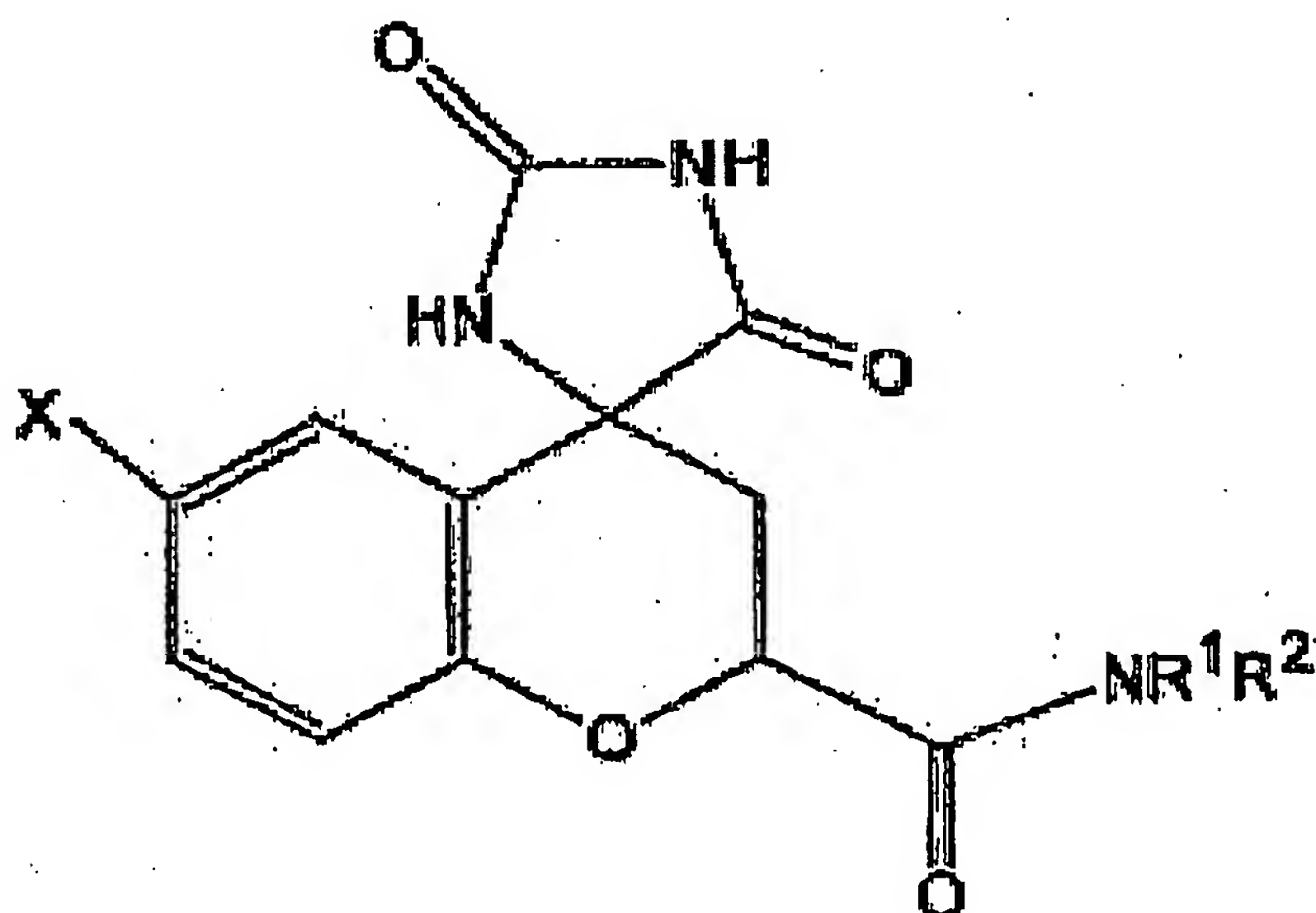
5 (wherein X represents a halogen or a hydrogen atom, R¹ and R² concurrently or differently represent a hydrogen atom or a C1 to C6 alkyl group, or R¹ and R² together with a nitrogen atom bound thereto and optionally another nitrogen atom or an oxygen atom, are combined to form a 5- to 6-membered heterocycle).

10 [Claim 6] The agent for improving visual acuity or inhibiting deterioration of visual acuity in diabetic maculopathy, according to claim 5, wherein the compound is (2S, 4S)-6-fluoro-2', 5'-dioxospiro [chroman-4, 4'-imidazolidine]-2-carboxamide.

15

【書類名】 手続補正書
【整理番号】 P 0 6 0 2 3 S K K
【提出日】 平成 1 9 年 8 月 3 日
【あて先】 特許庁長官 殿
【事件の表示】
【出願番号】 特願 2 0 0 5 - 5 1 7 5 0 2
【補正をする者】
【識別番号】 0 0 0 1 4 4 5 7 7
【氏名又は名称】 株式会社 三和化学研究所
【代理人】
【識別番号】 1 0 0 1 0 8 2 8 0
【弁理士】
【氏名又は名称】 小林 洋平
【電話番号】 0 5 4 9 - 2 7 - 5 5 1 5
【発送番号】 3 4 8 1 8 8
【手続補正 1】
【補正対象書類名】 特許請求の範囲
【補正対象項目名】 全文
【補正方法】 変更
【補正の内容】
【書類名】 特許請求の範囲
【請求項 1】 一般式
【化 1】

II(b)(iii)



(式中Xはハロゲン又は水素原子を意味し、R¹およびR²は、同時にあるいは別々に、水素原子、C1-6アルキル基を示すか、又は、R¹とR²は一緒にて窒素原子と共に或いは更に他の窒素原子又は酸素原子と共に5～6員の複素環を示す。)

で示される化合物を有効成分とする、糖尿病黄斑症の予防又は治療剤。

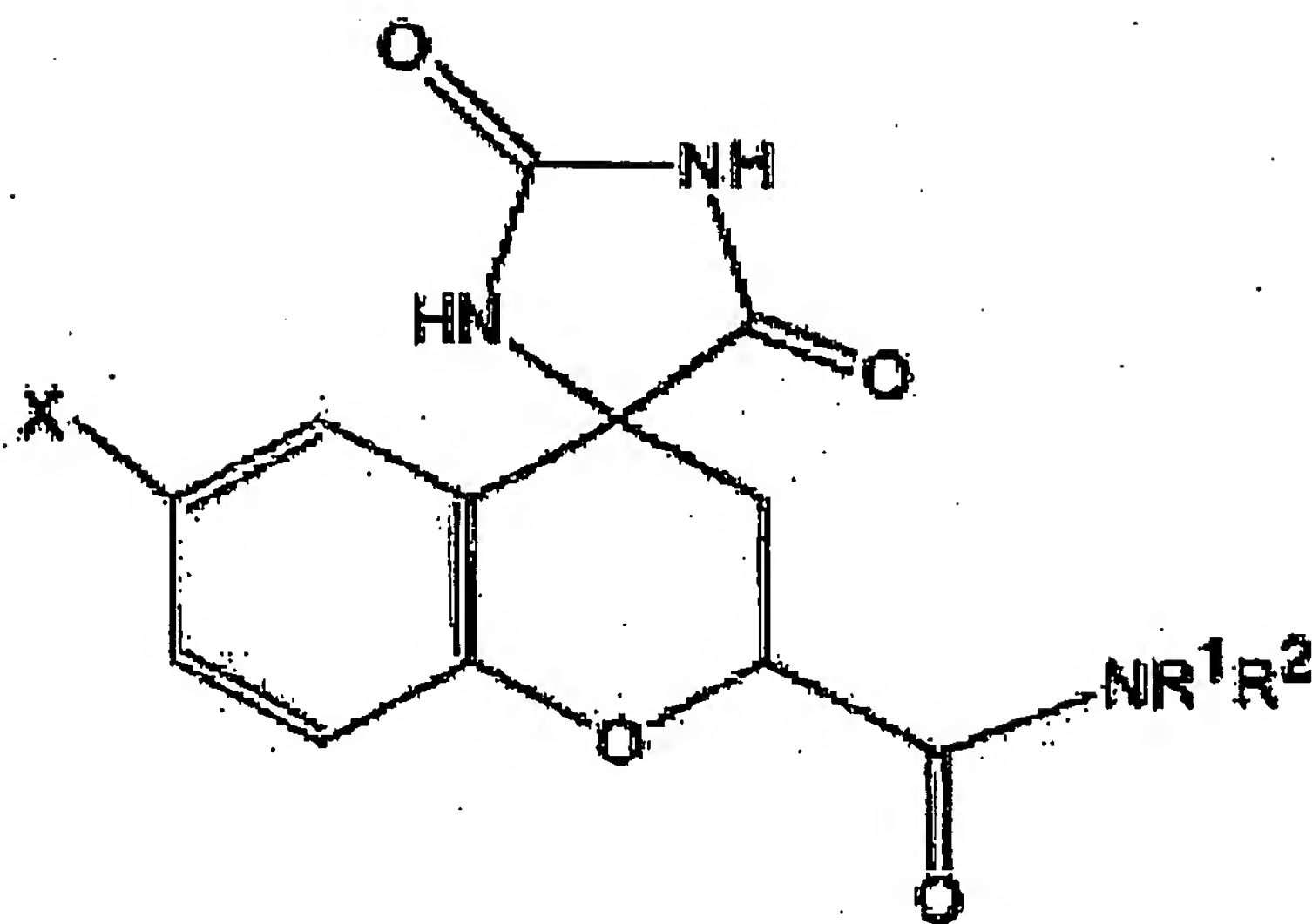
【請求項2】 化合物が(2S,4S)-6-フルオロ-2',5'-ジオキソスピロ[クロマン-4,4'-イミダゾリジン]-2-カルボキサミドである、請求項1に記載の糖尿病黄斑症の予防又は治療剤。

【請求項3】 糖尿病黄斑症における黄斑浮腫又は糖尿病色素上皮症に使用される、請求項1又は2に記載の糖尿病黄斑症の予防又は治療剤。

【請求項4】 糖尿病黄斑症における視力の改善又は低下防止剤として使用される、請求項1又は2に記載の糖尿病黄斑症の予防又は治療剤。

【請求項5】 一般式

【化2】



(式中Xはハロゲン又は水素原子を意味し、R¹およびR²は、同時にあるいは別々に、水素原子、C1-6アルキル基を示すか、又は、R¹とR²は一緒にて窒素原子と共に或いは更に他の窒素原子又は酸素原子と共に5～6員の複素環を示す。)

で示される化合物を有効成分とする、糖尿病黄斑症における視力の改善又は低下防止剤。

【請求項6】 化合物が(2S,4S)-6-フルオロ-2',5'-ジオキソスピロ[クロマン-4,4'-イミダゾリジン]-2-カルボキサミドである、請求項5に記載の糖尿病黄斑症における視力の改善又は低下防止剤。

Disclaimer:

This English translation is produced by machine translation and may contain errors. The JPO, the INPIT, and those who drafted this document in the original language are not responsible for the result of the translation.

Notes:

1. Untranslatable words are replaced with asterisks (****).
2. Texts in the figures are not translated and shown as it is.

Translated: 22:41:03 JST 01/07/2008

Dictionary: Last updated 12/14/2007 / Priority:

Decision to Grant a Patent

Application number: Application for patent 2005-517502

Date of Drafting: Heisei 19(2007) August 27

Patent examiner: TOMA, Hirofumi 3543 4C00

Title of invention: Prevention or the medical treatment agent of diabetic maculopathy

The number of claims: 6

Applicant: SANWA KAGAKU KENKYUSHO CO. LTD.

Representative: KOBAYASHI, Youhei

About this application, since no Reason for refusal is found, a Decision to Grant a Patent is carried out.

Director General(p.p.) Director(p.p.) Examiner Assistant examiner Manager for Determination
of Classification OHTAKU, Ikuji TOMA, Hirofumi TSURUMI, Hidenori 8829 3543 8415

1. Distinction of Patent: Usually

2. Reference documents: **

3. Application of Patent Law, Section 30: Nothing

4. Change of Title of Invention: Nothing

5. International Patent Classification (IPC)

C07D491/107 , A61K 31/4166 , A61P 3/10 , A61P 27/02

6. Deposition of Microorganism

7. Display of Purport that Retroactivity of Filing Date is not Accepted

Decision to Grant a Patent(Memorandum)

Application number: Application for patent 2005-517502

1. Technical Fields to Be Searched (IPC, DB Name)

C07D 491/107 A61K 31/33-33/44A61P 27/02 A61P 3/10 CAplus(STN)CAOLD(STN)
REGISTRY(STN)MEDLINE(STN)BIOSIS(STN)EMBASE(STN)WPIDS(STN)

2. Reference patent documents

JP,07-242547,A (JP, A)

3. Reference books and magazines

SPEICHER, M.A.et al., and Expert Opinion on Emerging Drugs, 2003, Vol.8/No.1 and p.239-
250AKITA, M.et al., Acta.Med.Okayama, 1993, and Vol.47/No.5 and p.299-
304GIANNOUKAKIS, N. -- [Current Opinion in] Investigational Drugs, 2003, Vol.4/No.10 and
p.1233-1239FERRIS, III, F.L., Survey of Ophthalmology, 2002, Vol.47/Suppl.2, p.S237

[Translation done.]

(English translation)

Reference: Dispatch No. 348188 Dispatch Date:05/09/2007

NOTIFICATION OF ALLOWANCE

Patent Application No. Patent Application No. 2005-517502
Drafting Date 27th August 2007
Examiner of JPO Hirofumi TOUMA, Serial No. 3543-4C00
Title of the Invention PROPHYLACTIC OR THERAPEUTIC AGENT
FOR DIABETIC MACULOPATHY
Number of Claims 6
Patent Applicant SANWA KAGAKU KENKYUSHO CO., LTD.
Representative of Applicant Yohei KOBAYASHI

This application is decided to be allowed since no reason for refusal has been found.

It is attested that the foregoing is the same as recorded on the file.

Date of attestation: 29th August 2007

Administrative Official of Ministry of Economy, Trade and Industry, Emiko HIRASE

Note: The patent fee must be paid within 30 days upon receipt of this communication.

整理番号: 発送番号:436492 発送日:平成19年 9月 5日 1/E

特許査定

特許出願の番号	特願2005-517502
起案日	平成19年 8月27日
特許庁審査官	當麻 博文 3543 4C00
発明の名称	糖尿病黄斑症の予防又は治療剤
請求項の数	6
特許出願人	株式会社三和化学研究所
代理人	小林 洋平

この出願については、拒絶の理由を発見しないから、特許査定をします。

上記はファイルに記録されている事項と相違ないことを認証する。

認証日 平成19年 8月29日 経済産業事務官 平瀬 恵美子

注意：この書面を受け取った日から30日以内に特許料の納付が必要です。

I(a)(ii)

Practitioner's Docket No.: 868_012

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of: Noriaki KATO, Hiroshi NAGANO, Kaori TANIKO and
Takahito JOMORI

Ser. No.: 10/587,320

Art Unit: 4173

Filed: May 10, 2007

Examiner: Nissa M. Westerberg

Confirmation No.: 4731

For: PROPHYLACTIC OR THERAPEUTIC AGENT FOR DIABETIC
MACULOPATHY

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

Sir:

Enclosed are copies of References AC through AL which were previously cited in an Information Disclosure Statement filed July 26, 2006.

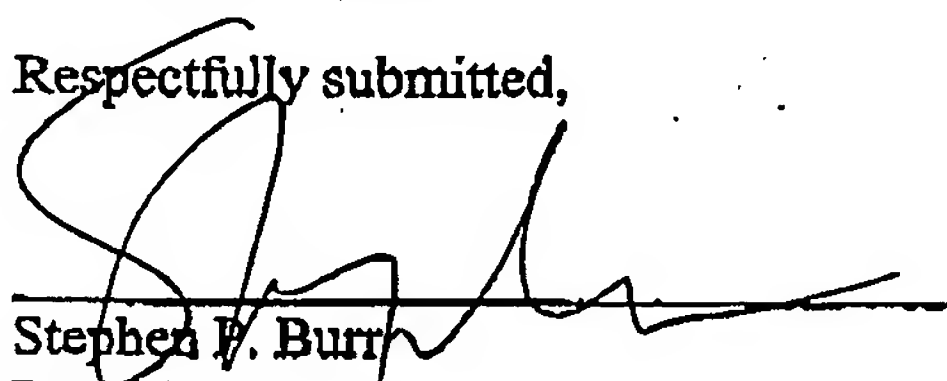
Pursuant to 37 CFR §1.56, the attention of the Patent and Trademark Office is hereby directed to newly cited non-patent literature References AM and AN as listed on the attached Form PTO-1449. Required copies of these references are also attached.

The above information is presented so that the Patent and Trademark Office may, in the first instance, determine any materiality thereof to the claimed invention. It is respectfully requested that the information be expressly considered during the prosecution of this application, and that these references be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

The Commissioner is hereby authorized to charge any additional fees associated with this communication or credit any overpayment to Deposit Account No. 50-1446.

Respectfully submitted,

December 18, 2007
Date


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Form PTO-1449 US DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(use as many sheets as necessary)</i>				<i>Complete if Known</i>	
				Application Number	10/587,320
				Filing Date	May 10, 2007
				First Named Inventor	Noriaki KATO
				Art Unit	4173
				Examiner Name	Nissa M. Westerberg
				Confirmation No.	4731
Sheet	1	of	1	Attorney Docket No.	868_012

U.S. PATENT DOCUMENTS

Exam Initial		Document Number	Date	Name	Our Docket No.	Class	Sub Class	Filing Date
	AA	6,479,729	11-12-2002	Campochiaro et al.				
	AB	4,740,517	04-26-1988	Kurono et al.				

FOREIGN PATENT DOCUMENTS

		Document Number	Date	Country	Class	Sub Class	Translation	Abstract
	AC	07-242547 A1	09-19-1995	JP				
	AD	61-200991 A1	09-10-1986	JP				
	AE	03-072226 B2	11-18-1991	JP				
	AF	08-231549 A1	09-10-1996	JP				
	AG	0 719 556 A2	07-03-1996	EP				

OTHER DOCUMENTS

(Including Author, Title, Date, Pertinent Pages etc.)

	AH	Speicher, Matthew A. et al., "Pharmacologic Therapy for Diabetic Retinopathy," Expert Opinion on Emerging Drugs, Vol. 8, No. 1 (2003), pages 239-250
	AI	Masahiko Akita et al., "Effects of and Aldose Reductase Inhibitor, SNK-860, on the Histopathological Changes of Retinal Tissues in a Streptozotocin-Induced Rat Model," Acta Med. Okayama, Vol. 47, No. 5 (1993), pages 299-304
	AJ	Irina G. Obrosova et al., "Aldose Reductase Inhibitor Fidarestat Prevents Retinal Oxidative Stress and Vascular Endothelial Growth Factor Overexpression in Streptozotocin-Diabetic Rats," Diabetes, Vol. 52, No. 3 (2003), pages 864 to 871
	AK	Giebel, S.J. et al., "Upregulation of Extracellular Proteinases and Angiopoietin 2 during Blood-Retinal-Barrier Alteration in the Diabetic Rat Model," ARVO Annual Meeting Abstract Search and Program Planner, Vol. 2003, pp. Abstract No. 3903
	AL	Sima, J. et al., "Angiostatin Decrease Vascular Leakage by Down-Regulating VEGF Expression," ARVO Annual Meeting Abstract Search and Program Planner, Vol. 2003, pp. Abstract No. 363.
	AM	Nick Giannoukakis, Fidarestat, Sanwa Kagaku/NCCurex/Sankyo, Current Opinion in Investigational Drugs, 2003, Vol. 4, No. 10, pp. 1233-1239.
	AN	Frederick L. Ferris, III, MD, "Evaluation of New Treatment Paradigms for Diabetic Retinopathy and Macular Edema," Survey of Ophthalmology, Volume 47, Supplement 2, December 2002, p. S237.

Examiner:		Date Considered:	
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EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Practitioner's Docket No.: 868_012

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SUPPLEMENTAL PRELIMINARY AMENDMENT

Sir:

Further to the Preliminary Amendment filed July 26, 2006, Applicants wish to further amend the subject application as follows:

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 4 of this paper.

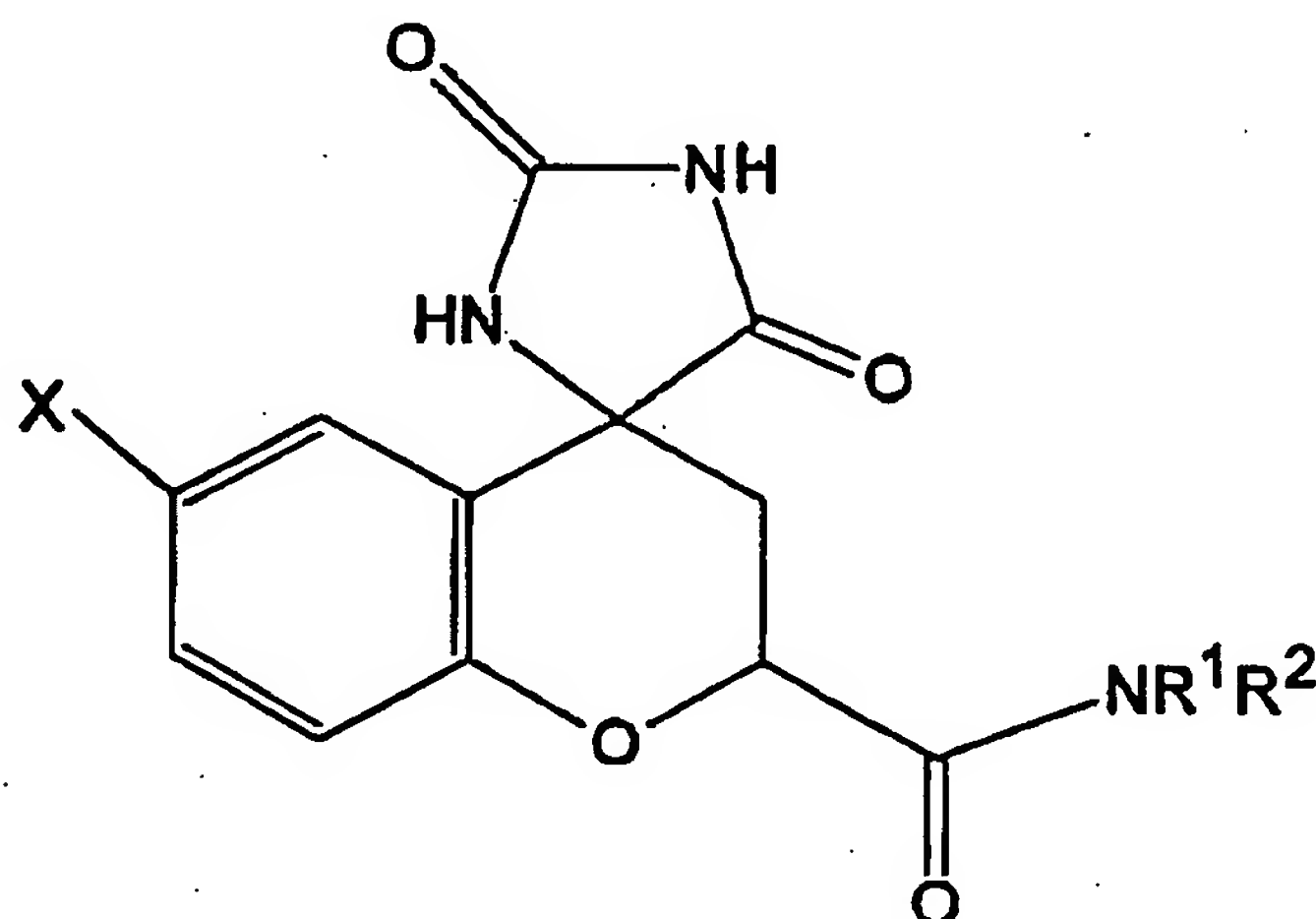
Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

Claims 1-9 (Cancelled).

10. (Currently Amended) A method for preventing/ameliorating diabetic maculopathy in a mammal comprising administering to the subject an effective amount of a compound represented by the following general formula:



wherein X represents a halogen or a hydrogen atom, R¹ and R² concurrently or differently represent a hydrogen atom or an optionally substituted a C1 to C6 alkyl group, or R¹ and R², together with a nitrogen atom bound thereto and optionally another nitrogen atom or an oxygen atom, are combined to form a 5- to 6-membered heterocycle.

11. (Previously Presented) The method for preventing/ameliorating diabetic maculopathy according to claim 10, wherein the compound is administered in the form of an oral agent.

12. (Previously Presented) The method for preventing/ameliorating diabetic maculopathy according to claim 10, wherein the compound is (2S, 4S)-6-fluoro-2',5'-dioxospiro [chroman-4,4'-imidazolidine]-2-carboxamide.

13. (Currently Amended) The method for preventing/ameliorating diabetic maculopathy according to claim 10, which is [[used]] for use in treating macular edema or retinal pigment epitheliopathy in diabetic maculopathy.

14. (Currently Amended) The method for preventing/ameliorating diabetic maculopathy according to claim 10, which is [[used]] for use in improving visual acuity or inhibiting a deterioration of visual acuity in diabetic maculopathy.

Claims 15-17 (Cancelled).

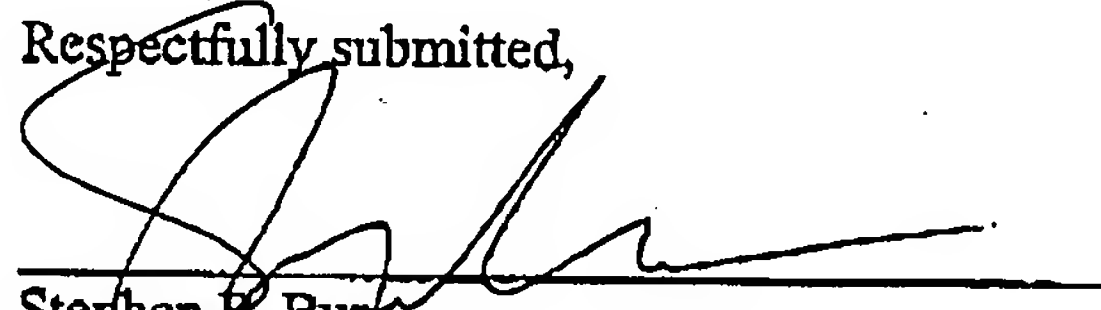
REMARKS/ARGUMENTS

Claims 10-14 are pending herein. Claims 15-17 have been cancelled without prejudice or disclaimer. Claim 10 has been amended to essentially correspond to independent claim 1 that was allowed in the corresponding Japanese National Phase Application (JP 2005-517502). No new matter has been added. Applicants believe the case is now in condition for examination.

If the Examiner believes that contact with Applicants' attorney would be advantageous toward the disposition of this case, he is herein requested to call Applicants' attorney at the phone number noted below.

The Commissioner is hereby authorized to charge any additional fees associated with this communication or credit any overpayment to Deposit Account No. 50-1446.

Respectfully submitted,


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December 18, 2007
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